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Short-Term Functional Plasticity of Cortical and Thalamic Sensory Representations and Its Implication for Information Processing

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This chapter surveys our recent findings on short-term cortical plasticity as induced by coactivation input patterns, discusses the functional aspects of this type of adult cortical plasticity and the possible implications for strategies of information processing, and outlines a hypothesis that attempts to integrate plastic-adaptive processes as inherent parts of normal on-line information processing.

There is now general agreement that plastic episodes are not limited to the critical developmental periods (Fig. 1). In describing reorganizational changes of adult plasticity it appeared useful to distinguish between two different forms. There is a remarkable reorganizational potential after injuries and lesions, either induced centrally or at the periphery (1–10). This type of plasticity is closely related to aspects of compensation and repair of functions that are impaired as a consequence of the injury. On the other hand, training and learning is known to induce powerful reorganizational changes similar in extent to those following injuries, which is referred to as use- and experience-dependent plasticity (11–20). In any way, a multiplicity of time scales on which reorganizations occur are involved suggesting a multiplicity of mechanisms. These latter findings extend plastic reorganizational processes to the field of higher cognitive functions related to learning and implicit memory functions. Use- and experience-dependent cortical plasticity may therefore represent the neural basis of lifelong adaptive sensory and perceptual capacities.

INDUCTION OF SHORT-TERM PLASTICITY

Generally, our approach enables us to study phenomena, constraints, rules, and implications of cortical plastic reorganizations in adult animals in the intact nervous system under acute experimental conditions. Fast and reversible cortical and subcortical reorganizations including both receptive fields and cortical representational maps were induced by two protocols: intracortical microstimulation (ICMS), and an associative pairing paradigm of tactile stimulation—paired peripheral tactile stimulation (PPTS). Both protocols have in common that the plastic changes are presumably induced by affecting the degree of synchronized neural activity. In the ICMS experiments, repetitive electrical pulse trains were delivered via a microelectrode to generate temporal synchronized discharges. The PPTS experiments were motivated by the Hebbian postulate according to which temporal coincidence of inputs are a theoretical prerequisite to change synaptic excit-

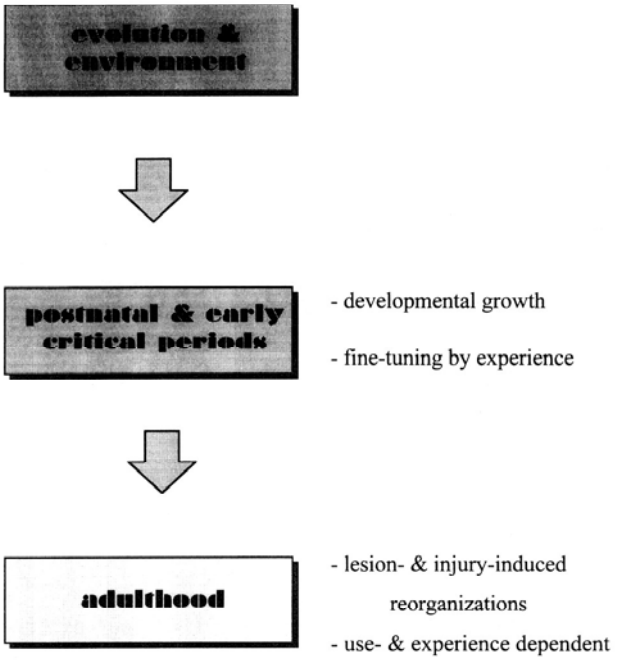


FIG. 1. Periods and episodes of neuronal plasticity.

ability (21). Temporally coherent inputs were provided by the associative pairing of simultaneously applied tactile stimulation at two different skin sites (22–25), which opens the possibility to study *in vivo* constraints of Hebbian types of plasticity.

The main difference between the two protocols is that PPTS involves the entire sensory pathway. Therefore, plastic changes can be supposed to occur to various degrees at subcortical and even lower levels. Also, PPTS offers the means to study possible psychophysical and perceptual consequences of short-term cortical reorganizations.

In contrast, the ICMS protocol offers the advantage of investigating locally the capacities and properties of functional plasticity, regardless of effects from the sensory periphery and the ascending pathways (26–32). Assuming that both methods are capable of generating reorganization of receptive fields and representational maps, one crucial question is how these changes are related to strategies of information processing; in other words, What is the impact of reorganized maps on the way in which information is processed and consequently on behavioral and perceptual performances?

METHODOLOGIC CONSIDERATIONS

Receptive fields, representational maps, and neural responses to computer-controlled tactile stimulation in the fore- and hindpaw were recorded in primary somatosensory cortex (SI) and the thalamic ventral posterior lateral (VPL) nucleus in adult rats under urethane anesthesia with conventional electrophysiologic recording and mapping techniques. Data analysis was based on poststimulus time histograms (PSTHs). In addition, the new method of recording optically two-dimensional areas of reflectance changes of the so-called intrinsic signals was used. It is well accepted that the regions of reflectance changes correspond with high reliability and significance to areas of increased neural activity. In this way, representational maps can be measured simultaneously with high spatial resolution. Possible nonspecific effects of the procedures were ruled out in sham stimulation control experiments, in which the entire protocols were followed with the exception that no ICMS or PPTS, respectively, was applied. After 12 hours, mapping was repeated. The experimental setup is shown schematically in Fig. 2.

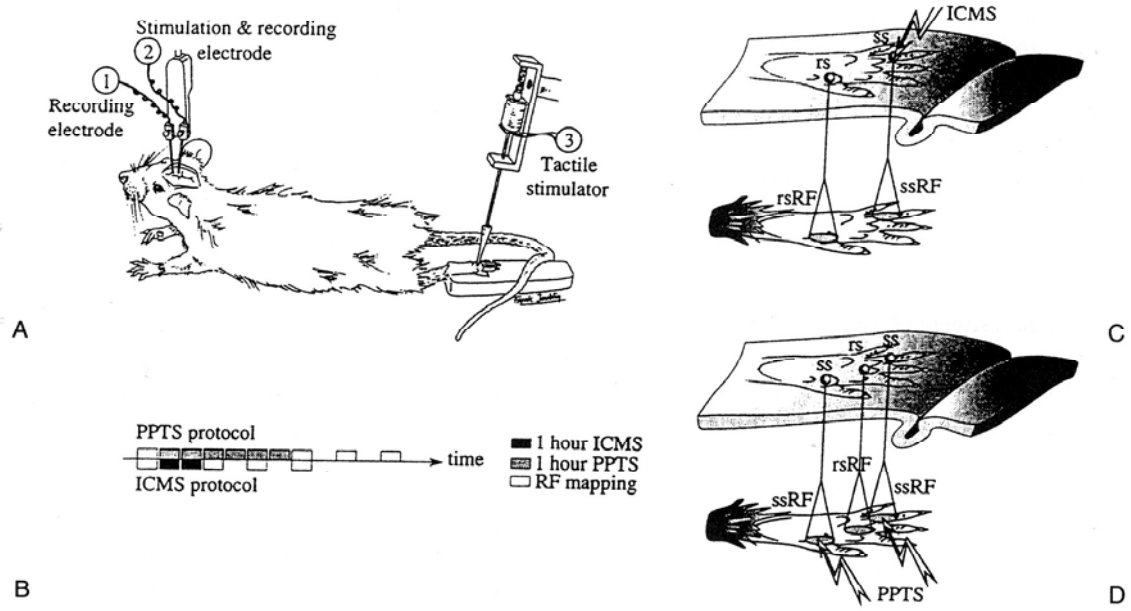


FIG. 2. Experimental setups. (**A**) Electrophysiologic recordings in the primary somatosensory cortex (SI) and stimulation devices. To induce cortical reorganization for ICMS experiments, one of the sites (1) was defined as the stimulation site and the other as the recording site (2); tactile stimulation was applied by a mechanical stimulator (3). In PPTS experiments, only one electrode was used to record in SI (1) and two (PPTS) tactile stimulators (3) were used during the experiment. (**B**) Time scale for ICMS and PPTS protocols and RF mapping procedures, before and after experimental manipulation. (**C, D**) Schematic drawing of cortical penetration sites—recording site (rs) and stimulation site (ss)—and cutaneous receptive fields (rsRF and ssRF) in an ICMS experiment (**C**) and in a PPTS experiment (**D**).

ICMS and PPTS Induction

ICMS was delivered with 13 pulses of 6 μA, 0.2 to 1 ms duration in 40-ms trains delivered at 1 Hz at a so-called stimulation site (ss), whose corresponding receptive field (RF) was denoted as ssRF. The other penetration sites were called recording sites (rs) that had corresponding rsRFs (cf. Fig. 2). To induce PPTS, the centers of two nonoverlapping receptive fields on two selected digits or on one digit and one pad were simultaneously stimulated for 6 or 15 hours according to the following protocol: A train of eight different interstimulus intervals between 100 and 3000 ms were used randomly followed by a pause of 15 s. After application of three trains there was an additional pause of 1 minute to avoid adaptation and habituation (see Fig. 7).

Correlated Activity

For analysis of correlated activity, we used two independent glass microelectrodes of various separation distances or solid-state multichannel microelectrodes consisting of four active sites arrayed along a straight line separated by distances of 80 μm (33). Spontaneous, ongoing activity was used for calculating cross-correlograms for delay times from −50 to +50 ms. Correlation strengths (CORR) were expressed as the differences of a weighted measure of peak area between an unshuffled and shuffled correlogram and varied between 0 and 1 for flat correlograms.

Laminar Analysis

Cortical hindpaw representations were mapped by penetrations perpendicular to the

cortical surface in supra- (II/III), infra-granular (V), and granular (IV) layers. After ICMS in layer IV or II/III, respectively, mapping was repeated at the identical sites recorded previously during premapping. Recording depths and laminar patterns were histologically verified.

Thalamic Recordings

To investigate constraints of subcortical plasticity, we extracellularly recorded neurons in the thalamic VPL nucleus. The somatosensory map in VPL was derived using a dorsoventral approach in single penetrations. Recording sites in VPL were histologically verified.

Optical Recordings

For optical measurements of intrinsic signals, we used a Lightstar II imaging and acquisition system (LaVision) with a 2-MHz A/D converter and a Peltier cooled, slow scan 12-bit digital CCD camera (34). The CCD was controlled by a 486 personal computer with 64 megabytes of random access memory. The cortex was illuminated either with a 546 or a 614 nm light source. Controls (nonstimulus conditions) were taken as blank images prior to each stimulus presentation. Images were computed by subtracting a stimulus from a nonstimulus condition. The spatial distributions of reflectance changes were color-coded and quantitatively computed in terms of cortical area for 25%, 50%, and 75% of the maximal reflectance changes.

Human Psychophysics

We tested right-handed human subjects in a tactile spatial discrimination task before and after a PPTS protocol of various durations. The index finger of the right hand was tested, and the middle finger of the right hand or the index finger of the left hand served as controls. We used eight distances between 0.7 and 2.5 mm. Each session consisted of 10 randomized presentations of each distance. The threshold was determined using a logistic fit function. Subjects who did not show normal learning rates and who did not reach a plateau of performance after 5 days were excluded from the analysis.

SHORT-TERM CORTICAL PLASTICITY AS INDUCED BY COACTIVATION INPUT PATTERNS

Under normal conditions, maps of the rat SI hindpaw representation are characterized by small, low-threshold, cutaneous receptive fields (RFs), located in a highly ordered manner on single digits, pads, or parts of the heel (Fig. 3), defining a fine-grained topographic representation. To induce fast and reversible functional reorganizations of receptive fields and representational maps by manipulating the efficiency of synaptic coupling in adult rat somatosensory cortex, we used two experimental protocols: ICMS and PPTS.

ICMS-Induced Postontogenetic Plasticity

ICMS-Induced Cortical Reorganizations of Receptive Fields and Maps

Application of 2 to 4 hours of ICMS in the center of the hindpaw representation caused an overall expansion of the representation. ICMS-affected receptive fields close to the microstimulation site were enlarged, showing low-threshold characteristics, and comprised skin sites on multiple digits, always including the microstimulation site RF (Fig. 3), which was increased by integration of the surrounding inputs. Similarly increased skin fields were found at recording sites close to the microstimulation site, revealing a distance-dependent, directed enlargement toward the control microstimulation site RF with the tendency to comprise it. The mean RF size increased severalfold after ICMS. Accordingly, the fine-grained topography of the hindpaw is replaced by a coarse representation of multiple skin sites, dominated by the representation of the microstimulation site RF. This was further substantiated by the analysis of the RF overlap, which increased similarly.

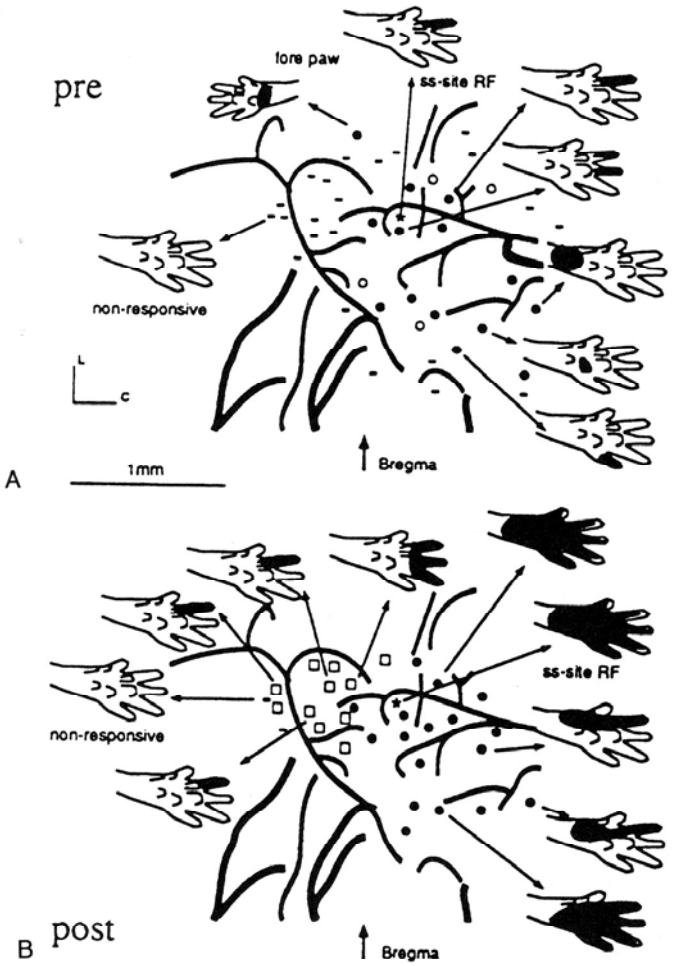


FIG. 3. (**A**) Control map (pre) of the hindpaw representation defined in rat primary somatosensory cortex based on a reconstruction of an enlarged brain photo. *Black lines* represent blood vessels, penetration sites are marked. Selected receptive fields (RFs) are drawn on sketches of the hindpaw. *Dark points* indicate cutaneous, *open circles* indicate noncutaneous responses, and *open squares* indicate newly induced cutaneous sites. *Bars* indicate locations where cells could not be driven by sensory inputs. For ICMS, a so-called microstimulation site RF (ssRF) on digit 2 was selected. (**B**) After 4 hours of ICMS, the border region and the central hindpaw representation was remapped (post). New skin representations containing the ssRF emerged up to 500 μm beyond the rostral boundary, while recording sites further rostrally maintained their unresponsiveness to tactile stimulation.

Generally, early ICMS-related effects could be detected after 15 min, and much greater effects were visible after 2 to 3 hours of ICMS. The changes were fully reversible within 6 to 8 hours after terminating ICMS (26,28–30).

Response latencies at rsRFs to ss stimulation were normally delayed in the range of 4 to 6 ms. After ICMS, they were considerably shortened and now came to match those measured at the ssRF, independent of the location of stimulation. Recording sites stimulated at the ssRFs before ICMS showed on the average 70% lower firing rates. After ICMS, these differences disappeared, indicating similar effectiveness of tactile stimulation at both recording sites (30). At the ss sites, response strengths were slightly reduced, but response latencies were not affected (Table 1).

TABLE 1. *Comparison of joint changes of different parameters during different types of plastic reorganization*

Parameter/ induction	Bicuculline	ICMS	Aging
RF size	Increase	Increase	Increase
Paired pulse—A_2/A_1	Facilitation	Facilitation	No effect
Paired pulse—A_{last}/A_1	Facilitation	No effect	Suppression
Response strength	Increase	Decrease	Decrease
Response latency	Shortening	No effect	Lengthening

ICMS-Induced Relocation of Areal Borders

Cortical reorganization of somatosensory maps in adult rats was not restricted to central, already cutaneous zones. A few hours of ICMS

at the rostral boundaries of the hindpaw representation generated plastic reorganization beyond these functionally defined representational borders by inducing new skin field representations in previously nonsomatic cortical regions, from where low-threshold movements could be elicited (Fig. 3). In this way, individually defined areal borders could be reversibly relocated over distances up to 800 μm, containing selectively skin field representations of the ICMS site. Response amplitude and latency characteristics of these newly induced recording sites resembled those recorded in the central representational zones (30).

Optical Imaging of ICMS-Induced Reorganizations of Cortical Maps

To visualize directly the effects of ICMS on the topography of cortical activity distributions evoked by circumscribed tactile stimulation to single digits or pads, we recorded optically reflectance changes before and after ICMS. In Fig. 4, maps of reflectance changes are shown that were obtained after stimulation of digit three. After 45 min of ICMS, a severalfold increase of the response area can be seen with full recovery after 60 min. The observed changes in response area using optical recording techniques were usually larger than those observed using electrophysiologic mapping techniques. Differences are most likely due to the different methods. In case of electrophysiologic mapping, only the so-called spiking point spread function, i.e., the spiking output of a cell, is assessed. In case of the optical recording, both pre- and postsynaptic activity, including subthreshold activity, is recorded. We believe that the use of optical imaging data can be helpful in unraveling the role of subthreshold and presynaptic activity with respect to plastic reorganization and possible mechanisms of plastic changes. In parallel studies of cortical topography using optical imaging, the notion of large and overlapping response areas was stressed (34–36), suggesting that the high degree of cortical overlap zones might provide a substrate for plastic reorganizations.

ICMS-Induced Cortical Reorganizations of Correlated Activity

Assuming that map changes reflect cooperative processing within a large number of single but interconnected elements, we investigated the temporal interactions of pairs of neurons during ICMS-induced plasticity by means of cross-correlogram analysis to describe quantitatively changes in neuronal cooperativity (26,29).

Correlated activity was measured before and after ICMS for pairs of neurons separated by different distances. These measurements revealed that correlated activity dropped to chance level at separations of 200 to 250 μm. After various periods of ICMS, correlation strength invariably increased for neuron pairs in this central zone. Most notable, however, was an emergence of correlated activity for neuron pairs separated by 300 to 800 μm or greater. This emergent functional coupling was similar in strength to that observed for the closely spaced neuron pairs in the central zone reported under control conditions.

Changes in correlated activity were related to changes of the underlying map by combining cross-correlogram analysis with mapping techniques. Changes of correlated activity were restricted to those regions of cortex that underwent reorganization of their skin representation. Increase of correlated activity was highest close to the stimulation site, but was also seen for neuron pairs more than 800 μm away from the stimulation site. On the other hand, when pairs were separated by only 300 to 400 μm, but one recording site was clearly outside the reorganized region, flat correlograms were obtained. We mostly observed broad peaks with a half-width of 10 to 20 ms that were always centered around $\tau = 0$.

We conclude that ICMS-induced plastic processes change the state of small neuron assemblies by changing the intrinsic temporal discharge patterns, supporting the idea that discharge coincidence plays a crucial role in the formation and modification of functional neuronal groups. Changes of correlated activity were also demonstrated to be dependent on an asso-

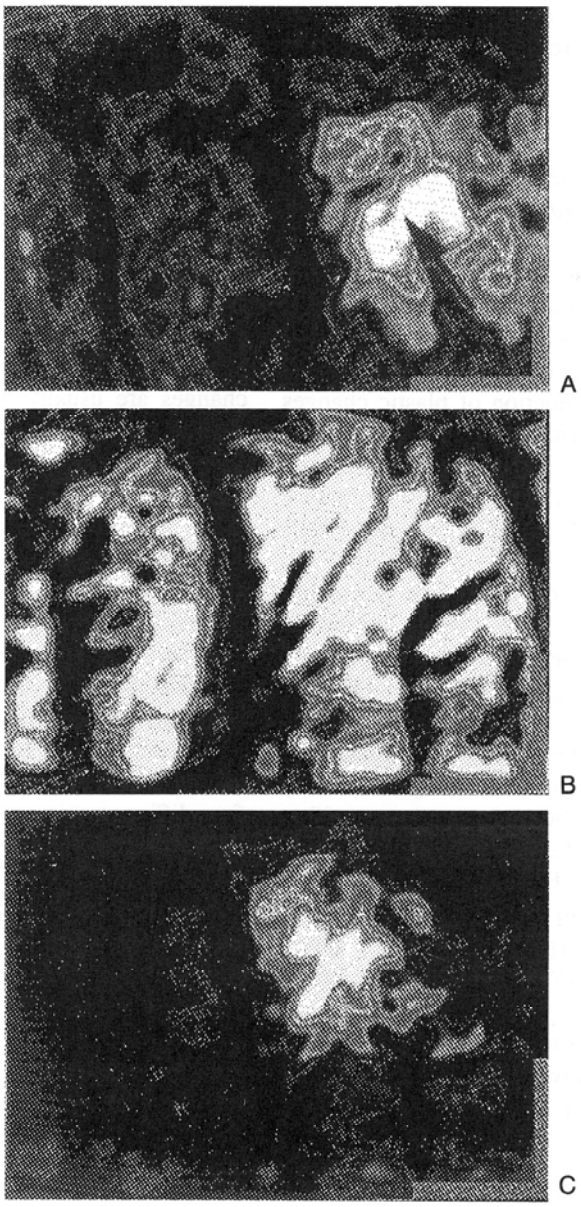


FIG. 4. Optical recordings of intrinsic signals following point-like tactile stimulation of the distal aspects of digit three in the hindpaw representation of rat primary somatosensory cortex. (**A**) Control. (**B**) Activity pattern after 45 minutes of ICMS (stimulation site marked by *arrow* in **A**). (**C**) Recovery 60 minutes after termination of ICMS. Scale bar = 1 mm, lateral, *up*; rostral, *left*.

ciative pairing protocol in behaving monkeys (37), indicating that changes of the type of functional connections between neuron pairs seem to be a general aspect of cortical plastic changes and therefore not accountable to the specific constraints of ICMS.

ICMS-Induced Lamina-Specific Reorganizations

Most studies about cortical plasticity observe plastic changes in cortical layer IV. Consequently, little is known about parallel changes in supra- and infragranular layers. Utilizing the local character of induction of plastic changes by ICMS, we performed a laminar analysis of plastic reorganizations by ICMS in layer IV and compared the evolving pattern to plastic changes induced following ICMS in layer II/III (31).

As a rule, the absolute RF size is systematically different in different layers. Also, the plastic effects following ICMS were highly layer specific. Following ICMS in layer IV, relative RF size changes were largest in layer IV and less severe in layers II/III and infragranular layers. While up to now following ICMS only RF enlargement had been observed, a considerable proportion of layer II/III cells showed also a reduction of their RFs (Fig. 5).

Following ICMS in layer II/III, a rather similar pattern of RF reorganization became apparent, in which layer IV cells showed the largest changes and supra- and infragranular layers much smaller changes. However, the effects of RF enlargement were on average only about 50% of those found after ICMS induction in layer IV.

The results indicate a clear layer-specific capacity of plastic reorganization after ICMS. Remarkably, neurons of the input layer IV appeared more sensitive to plastic changes than cells in the other laminae, specifically of II/III, which are assumed to play a crucial role in intracortical processing. Similarly, with regard to induction, layer IV was more effective, suggesting an overall specific role of layer IV neurons. It is an open question to what extent ICMS is sensitive to anatomical differences of the different layers such as afferent fiber patterns and cell type distributions, thereby producing the described lamina-specific changes. However, a similar role of layer IV neurons was recently described during plastic reorganization in different layers of auditory cortex during an auditory pairing paradigm (38).

ICMS-Induced Thalamic Reorganizations

The above-described experiments revealed rapid reorganizations of cortical representations of SI of adult rats following ICMS. These changes are usually interpreted as a result of fast modulation of Hebbian synapses within highly interactive cortical networks. However, while there is a substantial body of information about the reorganization at a cortical level, little is known about the nature of subcortical plasticity. We therefore attempted to further utilize the specific advantages of the local properties of ICMS to address the question of the nature of possible thalamic contributions to the cortical reorganization by studying plastic changes in the thalamic VPL nucleus (32). We modified the above-described ICMS technique and used four different protocols (Fig. 6A):

1. Intrathalamic stimulation (ITMS), to study its effects on VPL neurons.
2. ITMS, to study its effects on cortical neurons in SI.
3. ICMS, to study its effects on VPL neurons.
4. ICMS, to study its effects on cortical neurons in SI (standard protocol used in all previously described experiments).

In contrast to the well-known extensive cortical reorganizations following ICMS (protocol 4), using the analogous protocol (1 = microstimulation in VPL), only moderate, but highly significant effects in the reorganization of the somatosensory map at the thalamic level were found (Fig. 6B).

Protocols 2 and 3 were designed to explore the capacities of transfer of plastic changes either retrogradely (protocol 2) or anterogradely (protocol 3). Both protocols resulted in fairly

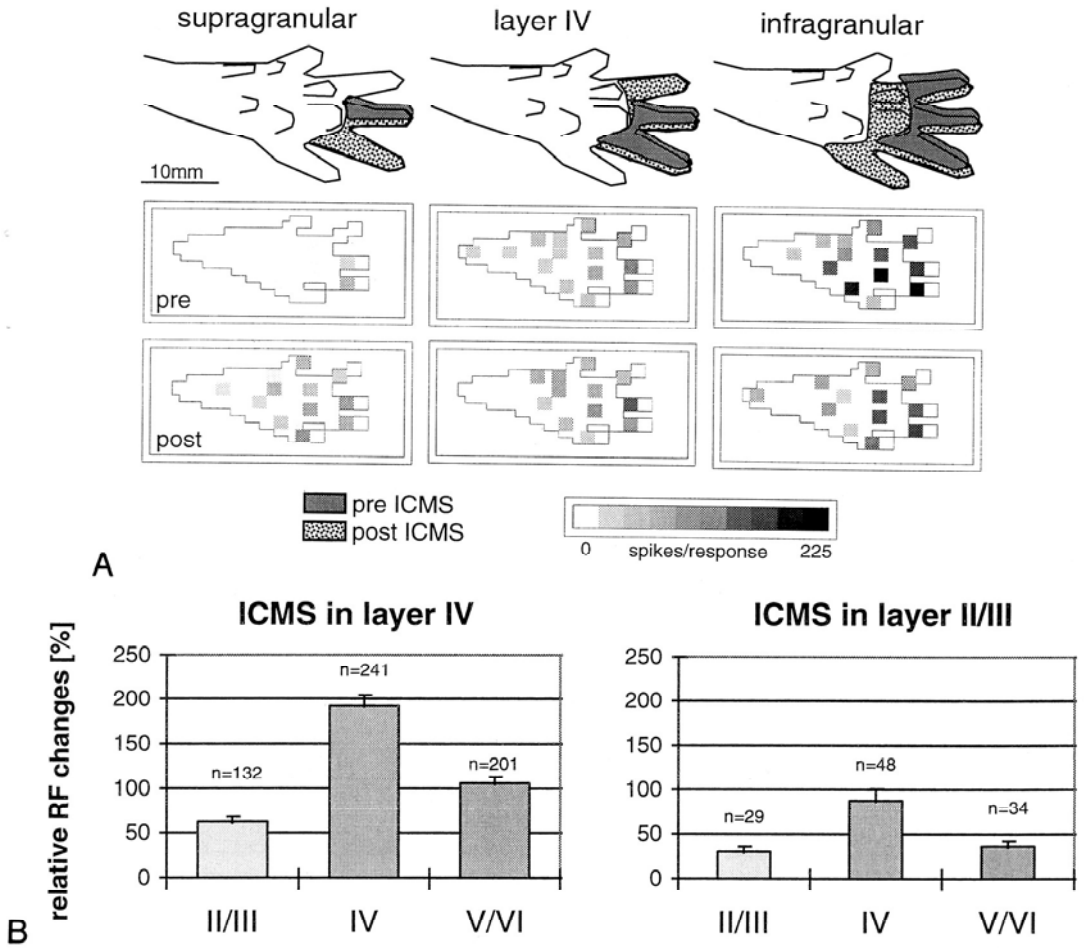


FIG. 5. (**A**) Examples of receptive fields (*top row*) and response planes (*lower rows*) recorded at the stimulation site in supragranular (*left*), granular (*middle*), and infragranular (*right*) layers before and after ICMS in layer IV. Control: dark hatching (*top row*) and *first row* of response planes. Post ICMS: light hatching (*top row*) and *bottom row* of response planes. (**B**) Mean relative changes of receptive field size recorded in layer II/III, IV, and V following ICMS in layer IV (*left*) and in layer II/III (*right*).

small changes. While ICMS in SI (protocol 3) resulted in significant enlargement of VPL RFs, the retrogradely induced changes by ITMS in SI (protocol 2) were not significant (Fig. 6B). Taken together, the results suggest that, using an identical induction protocol, thalamic neurons showed plastic changes of their RF sizes, but to a much smaller extent as compared with cortical changes. Within the constraints of the method, we were able to demonstrate a small, but significant corticothalamic transfer of short-term plastic effects from SI to VPL, but we could not detect significant evidence for a thalamocortical transfer.

As mentioned above in the context of layer-specific effects of ICMS, the same arguments concerning possible anatomic constraints hold for thalamic plasticity. However, in an analysis of plastic reorganization following modification of walking pattern in adult rats, substantial thalamic changes were observed starting about 2 weeks after manipulation that were comparable to the changes described after ITMS (39). In contrast, age-dependent reorganizations in VPL

A

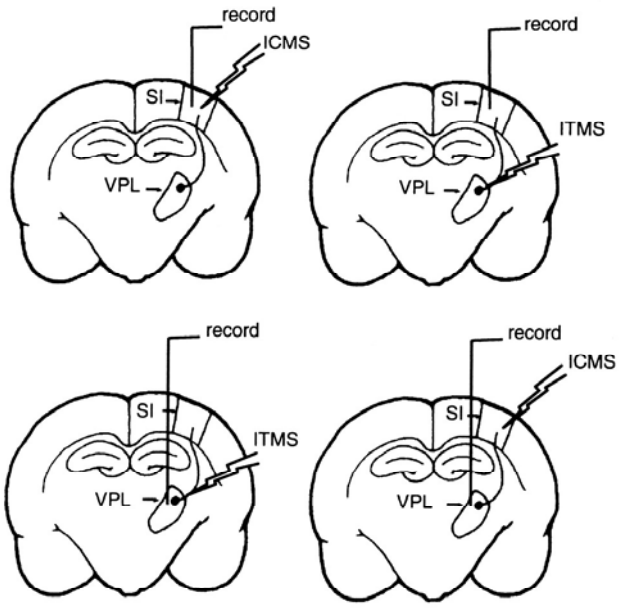
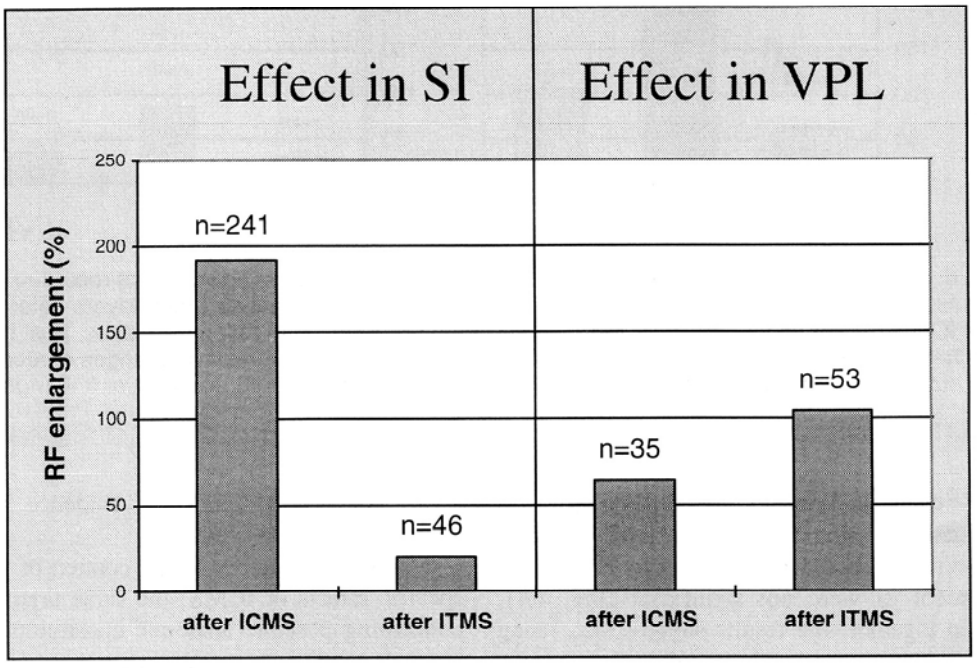


FIG. 6. (**A**) Schematic illustration of the four different protocols used. Indicated are the location of the recording (record) and the ICMS (intracortical) and ITMS (intrathalamic microstimulation) electrodes. SI, somatosensory cortex; VPL, thalamic ventral posterior lateral nucleus.

B



(**B**) Comparison of the mean percent changes of receptive field size following ICMS and ITMS in SI and VPL. Most dramatic changes were found for cortical plastic changes induced in SI. Level of significance: ICMS–SI: $p < .00001$; ITMS–SI: $p = .0685$; ITMS–VPL: $p < .0001$; ICMS–VPL: $p < .0001$.

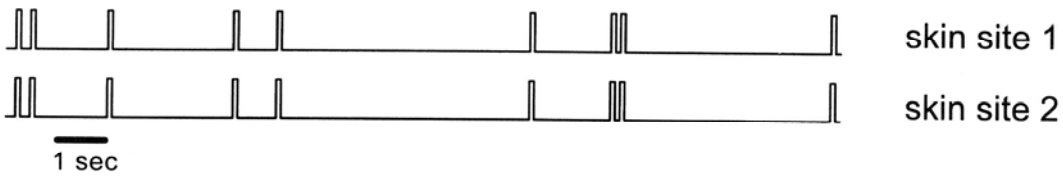


FIG. 7. Synchronous associative pairing of tactile stimulation. Illustration of the stimulus pattern used in the PPTS experiments.

in aged rats were comparable in extent to cortical changes, indicating considerable reorganizational capacities of thalamic neurons in an induction-dependent way (40,41).

PPTS-Induced Postontogenetic Plasticity

PPTS-Induced Cortical Reorganizations of Receptive Fields and Maps

Application of 6 to 12 hours of PPTS consisting of two simultaneously tactile stimuli to two digits or to one digit and to one pad (Fig. 7) caused substantial changes and overall expansions of the respective skin representations (22,23). These effects could be quantitatively described by the size of the cortical area representing the skin fields of selected digits before and after PPTS, which increased severalfold after PPTS (Fig. 8).

After PPTS, receptive fields showed normal, low-threshold cutaneous characteristics. However, RFs were increased in size by integration of the stimulated skin sites. Enlarged RFs were predominantly found close to the stimulation

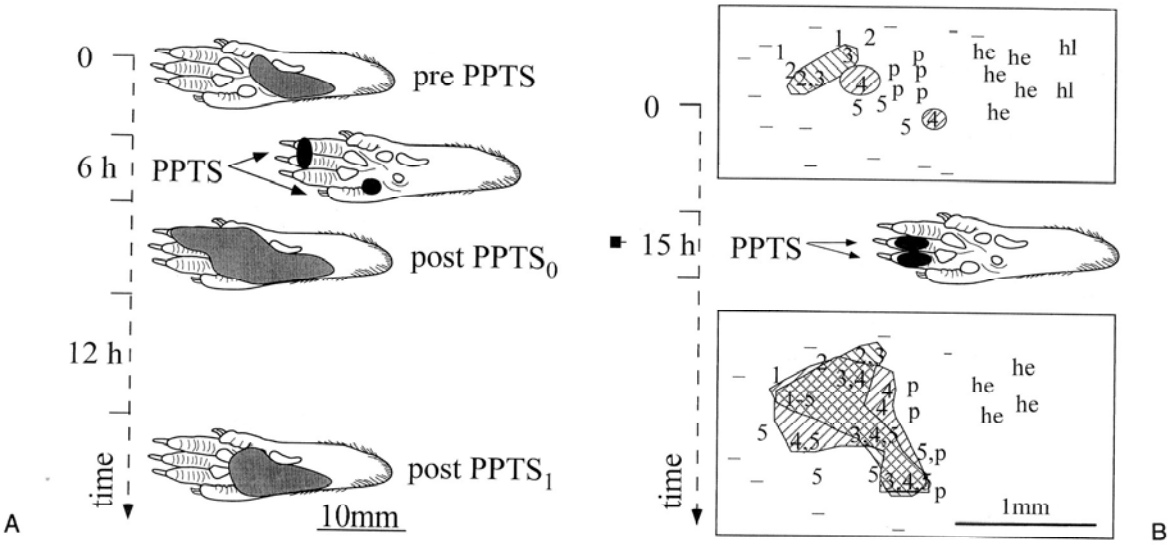


FIG. 8. (**A**) Cortical receptive fields before and after a 6-hour PPTS protocol. Under control, the receptive fields are located over the pad region. PPTS was applied at digits three and four and on the pad as indicated. After PPTS, receptive fields are enlarged, integrating skin field areas that were stimulated by the PPTS protocol. Twelve hours after terminating PPTS, receptive field size returns to control conditions, indicating reversibility of the effects. (**B**) Cortical reorganization after PPTS. Control map of the hindpaw representations of rat somatosensory cortex (*top*). Penetration sites are marked. Scale bar = 1 mm. Numbers indicate digits one to 5; p, pads; he, heel; hl, hindlimb. *Bars* indicate locations where cells could not be driven by sensory inputs. PPTS was applied for 15 hours on digits two and four. After PPTS (*bottom*), the profound reorganization is demonstrated by a severalfold enlargement of the PPTS stimulated skin sites that are highlighted by different hatching.

sites but also up to 500 μm away from them. This effect was selective, insofar as the enlargement always comprised both stimulated skin fields, which appeared to melt into each other. In addition, the degree of overlap of individual RFs with both RFs of the stimulated skin sites was affected, which doubled after PPTS. All effects were fully reversible 10 to 12 hours after terminating PPTS (Fig. 8).

PPTS-Induced Cortical Reorganizations of Response Dynamics

It has been demonstrated that neural responses to tactile stimulation depend decisively on their pharmacologic properties. Late response components were shown to be *N*-methyl-D-aspartate (NMDA) receptor dependent, while early response episodes were shown to be NMDA independent (42,43). It is conceivable that fast plastic reorganizational processes, such as those described here, are NMDA receptor mediated. We analyzed the temporal response properties of SI neurons to computer-controlled tactile stimulation to determine if the latencies and durations of the responses of cortical neurons were altered following PPTS. Response latencies that reflect early response components remained unchanged after PPTS. In contrast, the late, presumably NMDA receptor mediated, response components were much more pronounced after PPTS (22,23). This enhancement of NMDA receptor response components provide arguments for an involvement of glutamatergic synapses in PPTS induced plastic reorganizations.

PPTS-Induced Increase of Human Tactile Discrimination Performance

To explore the potential perceptual consequences of PPTS-induced short-term plastic processes, we studied tactile spatial two-point discrimination performance in human subjects (22,23,25) and used the two-point discrimination as a marker for the level of performance and degree of plastic changes. Here we address the question of the time course, reversibility, and persistence of PPTS-induced psychophysical threshold changes.

After 2 or 6 hours of a PPTS protocol analogous to the above-described electrophysiologic experiments (Fig. 7), we found a significant improvement in the spatial discrimination performance as indicated by decrease in discrimination thresholds. This effect could not significantly be elicited after 30 min of PPTS. Inspection of the thresholds of the nonstimulated control fingers revealed no changes (Fig. 9). Thresholds returned to normal 8 hours after terminating PPTS, indicating a full reversibility of the changes in discrimination threshold similar to that seen in the electrophysiology study.

To study possible long-term effects and possible effects of potentiation and accumulation of a repeated stimulation, we tested the discrimination threshold in a 3-day series in which the test subjects were stimulated each day for two hours. The observed increase of performance was unchanged by this protocol, but the effects persisted for 2 days.

These experiments indicate that the PPTS protocol is similarly effective in humans by improving the spatial discrimination performance. More generally, they support the notion that fast plastic processes have perceptual consequences. The problem arising concerning the relationship of parallel changes of receptive field sizes and discrimination thresholds is addressed below.

FUNCTIONAL ASPECTS OF SHORT-TERM CORTICAL PLASTICITY

General Properties of ICMS- and PPTS-Induced Plasticity

Our experimental data indicate that it is possible to study cortical plasticity under the constraints of acute experiments using anesthetized animals. Cortical reorganizations included typical signatures of cortical plasticity such as enlargement of RFs and representational areas. The fairly equivalent results of the ICMS and PPTS protocols provide further evidence for the assumption that the degree of coincidence of sensory stimulation is crucial to induce plastic

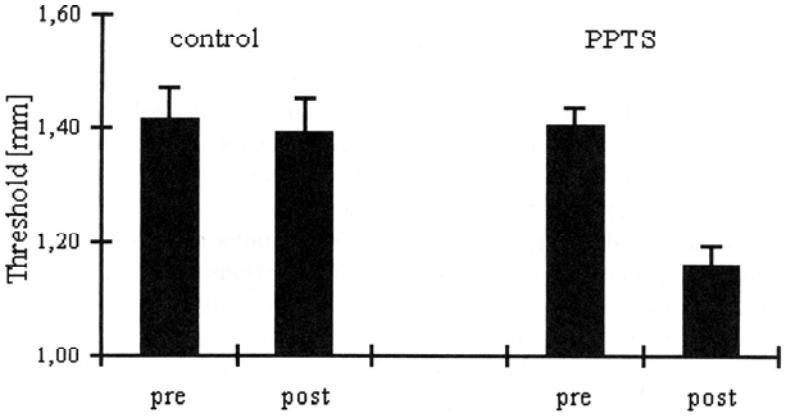


FIG. 9. Mean discrimination thresholds (mm) in skin surface of the control and stimulated fingers of 36 human subjects before and after 2 or 6 hours of PPTS.

changes. In case of ICMS, synchronous activity is induced directly by spreading electrical activity into a local group of neurons of the interconnected network. During PPTS, coincidence of firing is generated via the afferent pathway within two representational groups of simultaneously stimulated skin sites. In both cases the resulting coactivation patterns are then integrated into single representational units.

The behavioral relevance of PPTS could be directly demonstrated by inducing changes in the tactile discrimination performance. Although in this respect ICMS must be regarded as an artificial tool, its usage for stimulation of direction selective neurons in mediotemporal visual cortex (MT) during a motion detection task changed the animals' judgments toward the direction of motion encoded by the stimulated neurons, indicating that ICMS can directly influence behavior (44). Evidence for short-term learning within a few stimulus presentations was provided leading to significant improvement of perception (45,46). It can be concluded that both ICMS and PPTS represent general models of fast and reversible postontogenetic cortical plasticity with respect to learning and unlearning.

Time Course, Stability, and Reversibility of ICMS- and PPTS-Induced Plasticity

The observed changes of ICMS- and PPTS-induced plasticity are reversible on a time scale fairly proportional to that of induction. Long-term exposure to spatiotemporal input pattern is known to lead to persistent reorganizational changes such as in Braille readers and string players (16,18). In the case of string players, the amount of reorganization was proportional to the length of training (18). Taken together, several lines of evidence suggest that the stability of reorganization is related to the time course of induction.

The short time scale of the ICMS- and PPTS-induced effects and their reversibility support the hypotheses that this type of plasticity is mainly due to fast modulations of synaptic efficiency without necessarily involving anatomical changes. On the other hand, long-term reorganizations were shown to be paralleled by axonal and afferent sprouting (10,47). During which time period plastic changes are exclusively mediated by functional modulations of synaptic efficiencies remains an open question.

Are Learning Rules for Plastic Changes Exclusively Hebbian?

Coactivation patterns based on temporally coherent inputs provided by the simultaneous paired tactile stimulation at two different skin sites offer a tool to study *in vivo* constraints of Hebbian types of plasticity (48,49). The physiologic and psychophysical results are consistent with the hypothesis of correlational learning

rules. In addition, the above-described enhancement of late, NMDA receptor mediated response components (42,43) provide arguments for an involvement of glutamatergic synapses. It is conceivable that the sensitivity of temporal separations and the existence of local predictive learning rules (50) can be tested by introducing either temporal delays or desynchronized temporal patterns of stimulation between the two locations.

Theoretical work attempting to model different forms of cortical plasticity have stressed the need for a parallel implementation of both Hebbian and non-Hebbian learning rules (51–55). It should be noted that during the last several years, experimental evidence for non-Hebbian synaptic mechanisms has been accumulated (56–59). Our unpublished work suggests that with an asynchronous type of tactile pairing generating anticorrelated input patterns, plastic changes can also be induced that differ, however, in the overall properties of reorganization from those described for the simultaneous pairing of the PPTS protocol (Godde and Dinse, *unpublished data*).

The Role of Inhibition for Plastic Reorganizations

Since the early reports about receptive field size increases during plastic reorganizational processes, two possibilities have been discussed, according to which RF enlargement was hypothesized to be due to reduced inhibitory actions or to strengthening of excitatory connections. The first assumption was triggered by the observation that application of the γ-aminobutyric acid ($GABA_a$) antagonist bicuculline produces a strong RF enlargement (60–62).

Besides RF size changes, paired pulse behavior is often used as a marker of inhibitory mechanisms. Normally, the response to a second stimulus given at a sufficiently short interstimulus interval (ISI) is reduced compared with the first one. A decrease of this smaller reduction after a manipulation is referred to as paired pulse facilitation. We extended this approach by introducing trains of stimuli that facilitate differentiating between early, transient episodes of paired pulse behavior (response ratio between the second and first response) and a late episode (response ratio between the last and first response), reflecting the steady state characteristics.

On the other hand, cell injury in the context of brain lesions is known to produce profound hyperexcitability due to an aberrant release of glutamate (63). Using a systemic approach, increased excitability due to downregulation of inhibitory mechanisms cannot easily be distinguished from an augmented glutamate release. The use of antagonists of the putative neurotransmitters involved and a detailed analysis of effects based on a larger number of descriptors might be helpful to overcome these problems. The idea of Hebbian plasticity favors the concept of synaptic strengthening that requires involvement of excitatory, mainly glutamatergic mechanisms. The issue became more complicated by the observation that GABAergic mechanisms can directly affect and modulate NMDA receptor mediated changes of synaptic efficiency (64). While several lines of evidence support a decreased inhibitory action in lesion-induced reorganizations, the role of inhibition in mediating training and experience-related plastic changes is still unclear, indicating that lesion- and training-induced plastic reorganizations might reflect different forms of reorganizational plasticity.

Role of Representational Area Size and the Concept of Tasks

It is assumed that under normal processing conditions there exists a steady state of requirements that reflect the current adaptational profile of an individual organism to cope with the actual requirements of its environment. Only excessive deviations from this steady state can lead to measurable changes of the overall response properties. Once this steady state is passed, cortical reorganization is characterized by a selective expansion of cortical representations subject to increased use. This expansion is

regarded as beneficial in terms of performance without defining the consequences and implications of this enlargement. This assumption is complicated by the fact that increase of cortical areas occurs under quite different types of induction. The mere fact of higher and more intensive use leading to increase of cortical areas does not provide sufficient information about the specific requirement in terms of processing and about the nature and specificity of the task involved in the differential use. Therefore, cortical area enlargement can be regarded as a rather unspecific response. Due to the design of many experimental setups, the achievement of high spatial resolution is often conceived as a rather important and vital task. However, considering the environmental requirements, it appears conceivable that elaborated spatial resolution is only one important aspect among others, such as temporal resolution, texture and form discrimination, and control of fine movements. Under these assumptions, enlargement of cortical representational areas is difficult to interpret in terms of single elementary tasks. In this view, the final layout of cortical organization is not optimized to achieve high spatial resolution, but cortical enlargement is a complex compromise to achieve optimal performance within a broad spectrum of requirements of many different, even opposing tasks. As discussed below, similar considerations hold for RF sizes.

Role of Receptive Field Size

Under normal conditions, small receptive fields are believed to be correlated with high sensibility and low discrimination thresholds, as demonstrated by the progressive gradient of RF size from the distal to the proximal segments of the fingers (65). Cortical plastic reorganizations generally lead to an increase of receptive field size (66,67), fairly independent of the mode of induction. Increase of RF size was reported with one exception (68) following lesions (1–10), training (11–20), repetitive stimulation (69), ICMS (26–32), PPTS (22–25), modification of use (39), and even aging processes (40,41,70,71). This raises several possibilities: (i) all types of reorganizations are based on fairly identical mechanisms, (ii) the use of RF size as a marker of reorganizational changes provides only limited information because of its largely unspecific properties, and (iii) receptive field size in general is only indirectly and partially correlated with high performance of spatial acuity.

This problem becomes apparent when parallel reorganizational changes on a perceptual level have to be explained based on electrophysiologic data. For example, the PPTS-induced RF enlargement is paralleled by an increase of the spatial discrimination performance, an effect that can be explained by the assumption of a coarse coding processing scheme that utilizes the parallel increase of RF overlap and neuron number (see below). In contrast, RF enlargement observed during modified walking that leads to an impaired walking pattern (39), or during aging (40,41,70,71), or following lesions (1–10) is highly unlikely to be accompanied by an increase of discrimination performance. Alternatively, more, but hidden, parameters have to be assumed that are additionally affected by the plastic changes.

We investigated this possibility by introducing a broader spectrum of descriptors of plastic reorganizations. For example, we analyzed spatial and temporal integration properties, response latencies to tactile stimulation, and paired pulse behavior. Comparing the parallel effects of reorganization on RF size, response strength, latencies, and temporal integration properties, we can demonstrate that ICMS-induced plastic changes (25; Churs and Dinse, *unpublished data*), age-related plastic changes (41,70), and changes induced by application of bicuculline (72) differ significantly (Table 1).

Based on these findings it appears conceivable that when more than a single parameter is used, a more complete description of plastic changes can be accomplished. The ICMS data are characterized by a considerable variability, not typical for the bicuculline and aging experiments. A comparison of plastic changes of different parameters as illustrated in Table 1 indicates that in fact different types of inductions can be differentiated according to their joint

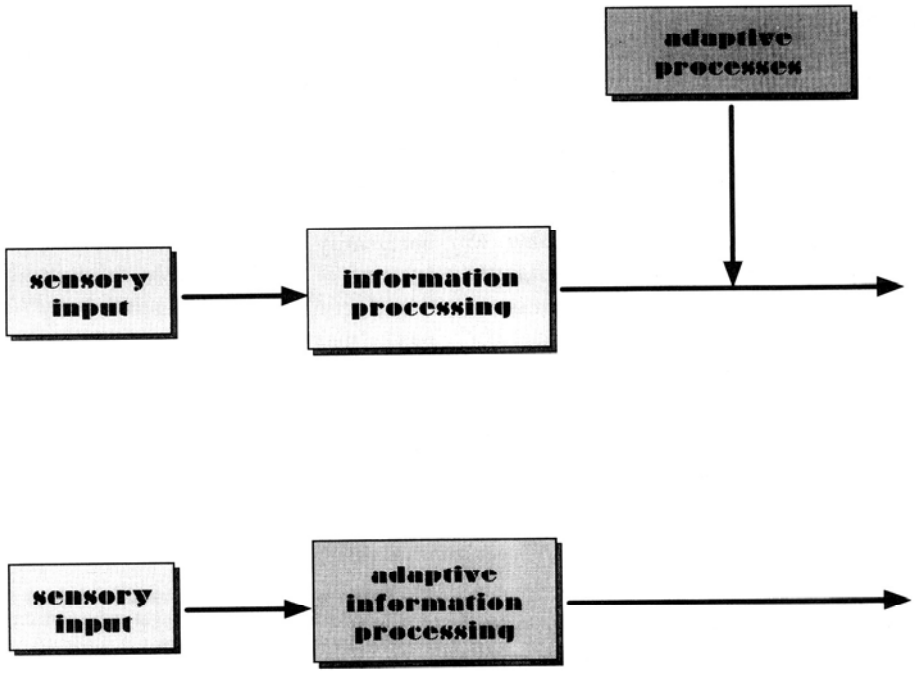


FIG. 10. Adaptive vs. invariant information processing.

richer description of plastic changes based on multiple parameters might be beneficial in differentiating and identifying types and forms of cortical plasticity.

Adaptive Information Processing vs. Separate Modules of Invariant Processing

Neural systems organize behavior according to the environmental conditions, which in turn affect the intensity and selection of input and sensory stimulation. However, as the environments and the constraints they impose change on a variety of time scales, each system operating in such an environment in fact preserves considerable lifelong adaptive capacities. In a general view, a parallel action of information processing and adaptation can be assumed, in which information processing is invariant against environmental changes. There is increasing evidence that adult reorganizational changes affect virtually all parameters and aspects known to be involved in information processing beyond RF size. Changes include correlated activity, RF dynamics, and temporal structure of the responses (77), RF properties such as orientation and directional tuning, spatial frequency and intensity sensitivity (78), spatial and temporal integration properties, and paired pulse behavior. As a consequence, it must be assumed that the entire mode of processing is changed. These changes are a reflection of parallel changes of perception and behavior, which in turn require an ongoing updating between neural and environmental changes to optimize processing. We therefore suggest a framework in which information processing is no longer invariant but plastic and able to adapt to ongoing changes in the environment (Fig. 10). In this view, no separate modules are needed. Instead, plastic-adaptive processes are integrated as an inherent part of normal on-line information processing providing a much higher degree of flexibility and efficiency.

CONCLUSIONS

Within dynamically maintained cortical networks a multiplicity of representational strate-

gies may provide solutions to process the diversity of sensory information, which varies in the temporal and spatial domain as well as in the behavioral relevance. As diverse as the processing strategies might be the range of underlying mechanisms of activity-dependent modulation of synaptic efficiency, according to Hebbian and non-Hebbian learning rules, leading to overall adaptational or compensational changes of cortical processing. It remains an open question how higher cortical levels can use and decode plastic changes that are due to ongoing changes of their input sources without jeopardizing the stability of processing and representation.

SUMMARY

We studied phenomena, constraints, rules, and implications of cortical plastic reorganization produced by input coactivation patterns in primary somatosensory cortex of adult rats. Intracortical microstimulation (ICMS) and an associative pairing of tactile stimulation (PPTS) induced plastic changes within minutes to hours that were fully reversible. Reorganization of receptive fields and topographic maps was studied with electrophysiologic recordings, mapping techniques, and optical imaging of intrinsic signals. Utilizing the specific advantages of local application of ICMS, we investigated lamina-specific properties of cortical representational plasticity, revealing a prominent role of the input layer IV during plastic reorganization. To study subcortical plasticity, we compared ICMS and intrathalamic microstimulation (ITMS), revealing robust thalamic reorganizations that were, however, much smaller than cortical changes. Using PPTS, we found significant reorganizational processes at the cortical level, including receptive fields, overlap, and cortical representational maps. The protocol was similarly effective at the perceptual level by enhancing the spatial discrimination performance in humans, suggesting that these particular fast plastic processes have perceptual consequences. The implications were discussed with respect to parallel changes of information processing strategies. We addressed the question of the possible role of RF size and size of cortical area, inhibitory mechanisms, and Hebbian and non-Hebbian learning rules. The short time scale of the effects and the aspect of reversibility support the hypothesis of fast modulations of synaptic efficiency without necessarily involving anatomic changes. Such systems of predominantly dynamically maintained cortical and adaptive processing networks may represent the neural basis for lifelong adaptational sensory and perceptual capacities and for compensational reorganizations following injuries.

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