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Plastic-adaptive properties of cortical areas

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14 Plastic-Adaptive Properties of Cortical Areas

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This chapter summarizes recent findings about plastic changes in adult early sensory and motor cortices. We discuss mechanisms leading to enduring changes of synaptic efficacy and of neural response behaviour in terms of receptive fields and cortical representational maps, with special emphasis on behavioural and perceptual consequences of cortical reorganizations, after peripheral lesion or injury, differential use and training. Given the assumption that the presence of plastic-adaptive abilities are a prerequisite for coping successfully with an ever-changing environment, we focus on comparative aspects, evaluating apparent similarities and dissimilarities emerging across different modalities. Most of the material reviewed is from animal studies that allow the study of adaptations and underlying mechanisms induced under a large variety of natural and laboratory conditions, at all levels from channels and synapses, to groups of neurones and cortical maps. Owing to the recent development of non-invasive imaging technologies, it has become possible to explore the significance of cortical plasticity for humans, occurring in "every-day-life". Massive and enduring reorganizations are present for all areas and modalities discussed, corroborating the view that cortical maps and response properties are in a permanent state of use-dependent fluctuation. We discuss various mechanisms controlling synaptic plasticity, the role of input statistics and attention, the top-down modulation of plastic changes, the "negative", (maladaptive) consequences of cortical reorganization, and the coding and decoding of adaptational processes. Despite the convincing evidence for profound reorganizational changes in all areas, specifically for injury-related plasticity, there exist also clear modality-specific differences, an observation holding at both the cellular and the systemic level. Differences include magnitude of changes, readiness of induceability and specificity of neural parameters that are affected. While reorganization of somatosensory and auditory cortex appears to follow comparable rules and constraints, adult visual cortex plasticity shows a number of particularities, indicating that visual cortical maps might be more difficult to change. We discuss a number of possible explanations based on different levels of abstraction. Among these are differences in control mechanisms of synaptic plasticity, the limiting character of complex topological maps, and the possible limitations of the metaphor of "use", as a driving force of adult plasticity.

KEYWORDS: Bienenstock-Cooper model, cortical map, Hebbian rules, input probability, lesion, LTP, LTD, maladaptivity, neural coding, perceptual learning, receptive field, sensory areas, simultaneity, synaptic plasticity, synaptic control mechanism, training, top-down modulation

1. GENERAL ASPECTS OF PLASTIC ADAPTIVE CAPACITIES

Heritable features evolving during evolutionary time spans are of ultimate advantage for survival and are, without exception, structurally fixed. To cope successfully with the ongoing changes of environmental conditions occurring during the lifespan of individuals, additional mechanisms are required that allow rapid and effective adaptations that are not specified by genetic constraints. In spite of the substantial amount of adaptational capacities, systems must possess sufficient generic stability to allow secure processing. Conceivably, there is a trade-off between modifiability and stability. In contrast to developmental plasticity, adaptations of adult brains do not, in the first place, rely on maturational and growth processes. Specifically, for learning-induced alterations there is a consensus that there is a crucial role for so-called functional plasticity, based on rapid and reversible modifications of synaptic efficacy. However, large-scale amputations have been shown to involve sprouting and outgrowth of afferent connections into neighbouring regions at cortical and subcortical levels (Florence *et al.*, 1998; Jain *et al.*, 2000). Technically, the term "adaptation" is used in a rather neutral sense, i.e. there are no implicit assumptions whether "adaptational changes" might yield a positive or negative outcome. Given this general overview, it appears conceivable that plastic-adaptive capacities of various forms represent a general and ubiquitous cortical feature present in all sensory modalities as well as in higher cortical areas. Before summarizing details and possible deviations from that scheme, some basic properties of cortical plasticity, observable in early sensory areas are briefly discussed.

1.1. Driving Forces that Lead to Adaptational Changes

What are crucial factors that are potentially effective in inducing changes of neural representations? We assume a dynamically-maintained steady state of representations that emerged during development and adulthood from maturational and learning processes, reflecting the history of adaptation to a "mean environment". *Mean environment* is defined as the accumulated and idiosyncratic experience of an individual. Adaptational processes are assumed to operate on these representations, and long-lasting changes are likely to occur when sensory input patterns are altered such that they deviate from the mean environment.

(a) A simple way to alter the average steady state is by changing the input statistics. Features that are specifically effective in driving adaptational changes are simultaneity, repetition, or more generally, spatio-temporal proximity. These changes occur without involving attention or other cognitive processes. Accordingly, a class of non-cognitive adaptations is largely based on bottom-up processing.
(b) Alternatively or additionally, attention can be drawn to a stimulus, thereby selecting it in comparison to others. Furthermore, the relevance of a stimulus can change dependent on context, history and behavioural task, thereby modifying the processing of the physically-defined attributes. There is general agreement that modification of early sensory processing by attention and stimulus relevance reflects top-down influences arising from cognitive processes.
(c) Reinforcement of learning processes by reward or punishment usually accelerates adaptational processes. Such influences are assumed to be mediated by specific brain regions modifying early sensory processing.

1.2. The Hebbian Metaphor

A central paradigm in the description and analysis of cortical plasticity is built around the Hebbian concept (1949) stating that episodes of high temporal correlation between pre- and postsynaptic activity are prerequisite for inducing changes of synaptic efficacy. Historically, the idea that cooperative processes are crucially involved in generating long-lasting changes of excitability can be traced back to the 19th century (James, 1890). In fact, since the time of Hebb, the aspect of simultaneity has become a metaphor in neural plasticity, although the exact role of Hebbian mechanisms in use-dependent plasticity remains controversial (Carew *et al*., 1984; Fox and Daw, 1993; Granger *et al*., 1994; Montague and Sejnowski, 1994; Joublin *et al*., 1996; Buonomano and Merzenich, 1996; Edeline, 1996; Cruikshank and Weinberger, 1996a,b; Ahissar *et al*., 1998). It has been suggested that the definition of Hebbian mechanisms must be extended beyond "simultaneity", in the sense of strict coincidence, to cover all facets arising from learning processes. Such a definition must include a large number of pre- and post synaptic patterns, as well as a broad time-window for what neural systems regard as "simultaneous".

1.3. Use-dependent Plasticity as a Basis for Perceptual and Motor Skills

One of the striking features of use-dependent plasticity is the correlation of cortical changes with performance. The acquisition of skills has often been used as an index for the build-up of implicit memories. Implicit memories are acquired automatically and without consciousness. Many repetitions, over a long time and without higher-level cognitive processes, are sufficient to improve perceptual and motor skills. This non-cognitive feature in combination with many repetitions characterizes an important aspect of use-dependent neural plasticity. It has been speculated that use-dependent plasticity might be strongly related to, if not a substrate for, implicit memory function.

1.4. Perceptual Learning

Perceptual learning is the ability to improve perceptual performance by training and practice (cf. Gibson, 1953). In this sense, perceptual learning occurs largely independent of conscious experience (cf. Fahle and Poggio, 2001). Perceptual learning is usually characterized by a high specificity to stimulus parameters such as location or orientation of a stimulus, with little generalization of what is learned to other locations or to other stimulus configurations. Selectivity and locality of this type implies that the underlying neural changes most probably occur within early cortical representations that contain well-ordered topographic maps to allow for this selectivity, but where generalization with respect to spatial location and orientation has not yet occurred. Transfer of newly acquired abilities is considered an important marker of that processing level at which changes are most likely to occur: limited generalization indicates high locality of effects in early representations. In contrast, transfer of learned abilities implies the involvement of higher processing levels, as is often observed in task and strategy learning. There is increasing evidence that changes in early cortical areas might be more directly linked to perceptual learning than previously thought (Karni and Sagi, 1991; Recanzone *et al*., 1992a; Schoups *et al*., 1995; Crist *et al*., 1997; Fahle, 1997; Fahle and Poggio, 2001). While there is a large literature on

perceptual learning in the visual system, much less data are available for comparable experiments in the auditory and somatosensory system.

2. POST-ONTOGENETIC PLASTICITY OF CORTICAL MAPS AND RECEPTIVE FIELDS

It is useful to distinguish between two different forms of adult plasticity:

- Lesion-induced plasticity subsumes the reorganization after injury and lesion, induced either centrally or at the periphery. This type of plasticity refers to aspects of compensation and repair of functions that have been acquired prior to injury or lesion.
- Training- and learning-induced reorganization is often denoted as "use-dependent plasticity" and describes plastic changes parallel to the behavioural improvement of performance, i.e. the acquisition of perceptual and motor skills.

In view of the fact that amputation changes the pattern of use entirely, a more accurate distinction would be between "lesion-induced" *vs* "non-lesion-induced" plasticity. Just how far the two forms are different, or possibly based on similar mechanisms, is a matter of ongoing debate.

There are a number of detailed reviews providing an excellent overview covering all facets of cortical plasticity in early sensory and motor areas (Merzenich *et al*., 1988; Kaas, 1991; Scheich *et al*., 1991; Eysel, 1992; Garraghty and Kaas, 1992; Sameshima and Merzenich, 1993; Donoghue, 1995; Weinberger, 1995; Cruishank and Weinberger, 1996a; Edeline, 1996; Dinse *et al*., 1997a; Kaas and Florence, 1997; Sanes and Donoghue, 1997; Buonomano and Merzenich, 1998; Gilbert, 1998; Nicolelis *et al*., 1998a; Rauschecker, 1999; Recanzone, 2000; Dinse and Merzenich, 2002). In the following, the main focus is on comparative aspects. It should be noted that this comparative approach is hindered by the fact that there are, with rare exceptions, few studies explicitly exploring possible area- and modality-specific properties of cortical plasticity.

2.1. Lesion-Induced Plasticity

Large-scale reorganizations were first described following digit amputation or deafferentation in the primary somatosensory cortex of cats, monkeys and racoons (Kalaska and Pomeranz, 1979; Kelahan *et al*., 1981; Rasmusson, 1982; Merzenich *et al*., 1983, 1984; Wall and Cusick, 1984; Calford and Tweedale, 1988; Florence and Kaas, 1995; Kaas *et al*., 1999). The main result was that the cortical territory representing the skin surface removed by amputation or deafferentation did not remain silent, but was activated by stimulation of bordering skin sites. Major topographic changes for cutaneous afferent representations were limited to a cortical zone extending about 1 mm on either side of the initial boundaries of the amputated digits. These early data indicated that the sensory cortical representations in adults were not hard-wired, but retain a self-organizing capacity operational throughout life (Merzenich *et al*., 1984).

Much more dramatic cortical reorganizations were reported after mapping the cortex of monkeys that had undergone deafferentation of the dorsal roots (C2-T4) several years before, thereby depriving a cortical area of over 1 cm^2 of its normal input from the arm and

hand (Pons *et al.*, 1991). These authors found that all of the deprived area had developed novel responses to neighbouring skin areas, including the face and chin. It is now well established that comparable large-scale remodeling occurs in human somatosensory and motor cortical areas, weeks or months following limb amputation (Fuhr *et al.*, 1992; Cohen *et al.*, 1993; Kew *et al.*, 1994; Yang *et al.*, 1994; Flor *et al.*, 1995, 1998; Knecht *et al.*, 1998) implying that similar (if not identical) rules govern lesion-induced plastic reorganizations in humans (see also section 2.5. "Therapeutic consequences of cortical plasticity").

A series of lesion experiments performed a couple of years later in auditory and visual system confirmed the tremendous capacities of the cortex for reorganization described for SI. Several months after a restricted unilateral lesion of the cochlear of guinea-pigs, the area of contralateral auditory cortex representing the lesioned frequency range was partly occupied by an expanded representation of sound frequencies adjacent to the lesioned frequency range. Thresholds at their new characteristic frequencies (CFs) were close to normal (Robertson and Irvine, 1989). In extending these experiments, it was found that unilateral restricted cochlear lesions in adult cats altered the topographic representations of the lesioned cochleas along the tonotopic axis of primary auditory cortex, extending up to 3 mm rostal to the area of normal representation, with no apparent topographic order within this enlarged representation (Rajan *et al.*, 1993). Interestingly, no comparable signs of plastic changes of the frequency map were found in the dorsal cochlear nucleus of adult cats following unilateral partial cochlear lesions (Rajan and Irvine, 1998). A striking over-representation of the frequency corresponding to the border area of the cochlear lesion has been observed after amikacin-induced cochlear lesions in primary auditory cortex of the adult chinchilla. The amount of reorganization was similar in extent to that previously seen during development (Kakigi *et al.*, 2000).

Fairly large lesions (5 by 10 degrees of visual angle) of the retina markedly altered the systematic representations of the contralateral eye in primary and secondary visual cortex, when matched inputs from the ipsilateral eye were also removed. Cortical neurones that normally have receptive fields in the lesioned region of the retina acquired new receptive fields in portions of the retina surrounding the lesions (Kaas *et al.*, 1990). In another study, removal of visual inputs by focal binocular retinal lesions resulted in an immediate increase in receptive field size for cortical cells with receptive fields near the edge of the retinal scotoma. After a few months even the cortical areas that were initially silenced by the lesion recovered visual activity, representing retinotopic loci surrounding the lesion (Gilbert and Wiesel, 1992). Anatomical studies showed that the spread of geniculocortical afferents is insufficient to account for the cortical recovery (Darian-Smith and Gilbert, 1995), indicating that the topographic reorganization within the cortex was largely due to synaptic changes intrinsic to the cortex, most probably through the system of long-range horizontal connections. In a series of studies, the reorganizational properties of adult visual cortex following various forms of retinal injuries and lesions has been well established (Schmid *et al.*, 1996; Calford *et al.*, 1999, 2000).

Quantitative studies of the response characteristics of visual neurones after retinal lesions indicated that these neurones develop fairly normal processing features. After three months of recovery, newly activated units exhibited strikingly normal orientation tuning, direction selectivity, and spatial frequency tuning, when high-contrast stimuli were used. However, contrast thresholds of most neurones were abnormally elevated, and the maximum response amplitude under optimal stimulus conditions was significantly reduced. The results suggest that the striate cortical neurones reactivated during topographic reorganization are

capable of sending functionally meaningful signals to more central structures, provided that the visual scene contains relatively high contrast images (Chino *et al.*, 1995).

In animals that were allowed to recover from a complete monocular deactivation for up to several months, there was also rearrangement of the retinotopic maps. However, in this case, most neurones in the deprived peripheral representation remained unresponsive to visual stimuli even more than one year after treatment (Rosa *et al.*, 1995). This is in marked contrast with the extensive reorganization that is observed in the central representation of V1 after restricted retinal lesions. The low potential for reorganization of the monocular sector of V1 demonstrates that the capacity for plasticity of mature sensory representations varies with location in cortex: even small pieces of cortex, such as the monocular crescent representations, may not reorganize completely if certain conditions are not met. These results suggest the existence of natural boundaries that may limit the process of reorganization of sensory representations.

Taken together, all sensory areas display a well-documented capacity for profound reorganizations following peripheral lesions. However, there might exist differences in the magnitude of changes. Whether this reflects some modality-specific limitation of the visual cortex to reorganize after large retinal lesions requires further investigations. (For a discussion of perceptual consequences of lesion-induced reorganizations, and general aspects of maladaptive consequences see also section 2.5. below "Therapeutic consequences of cortical plasticity").

2.2. Training- and Learning-Induced Use-Dependent Reorganization

Perceptual skills improve with training (cf. Gibson, 1953). Accordingly, one of the key questions in cortical plasticity is how cortical changes are linked to parallel changes of perceptual and/or motor performance. This question requires the simultaneous assessment of both neurophysiological and behavioural changes.

For example, Recanzone and coworkers showed that tactile frequency discrimination training in the adult owl monkeys over several months led to a significant reduction of frequency discrimination threshold (Recanzone *et al.*, 1992a). When the cortical areas representing the skin area of the trained fingers were mapped, large-scale cortical reorganization became apparent, which included changes of receptive fields and of topography of cortical representational maps. Most notable, there was a significant correlation between the enlargement of cortical territory representing the skin surface stimulated during training and the improvement in performance, indicating a close relationship between cortical and perceptual changes (Recanzone *et al.*, 1992b). In addition, sinusoidal stimulation of the trained skin elicited larger-amplitude responses, peak responses earlier in the stimulus cycle, and temporally sharper responses, than did stimulation applied to control skin sites. Analysis of cycle histograms for neuronal responses in area 3b revealed that the decreased variance of each stimulus cycle could account for behaviourally-measured frequency discrimination improvements (Recanzone *et al.*, 1992c). With the somatosensory system as an example, these data demonstrated for the first time a direct relation between cortical plasticity and improvement of performance.

A largely identical approach was taken for an analysis of training-induced changes in AI. Monkeys, trained for several weeks to discriminate small differences in the frequency of sequentially presented tonal stimuli, revealed a progressive improvement in performance with training. At the end of the training period, the tonotopic organization of Al was defined

electrophysiologically. The cortical representation, the sharpness of tuning, and the latency of the response were greater for the behaviourally-relevant frequencies of trained monkeys when compared to the same frequencies of control monkeys. Notably, the cortical area of representation was the only studied parameter that was correlated with behavioural performance. These results demonstrate that attended natural stimulation during a long-term training protocol can modify the tonotopic organization of Al in the adult primate, and that this alteration is correlated with changes in perceptual acuity (Recanzone *et al*., 1993).

While there is a large body of information about perceptual learning in the visual domain in human subjects (see also section 2.7), little is known about parallel changes in visual cortex. In a study on perceptual learning in humans (discrimination of orientations), subjects showed a marked improvement over days, which was highly specific for position and orientation (Vogels and Orban, 1985; Schoups *et al*., 1995). However, the precise nature of the accompanying changes still remains unclear. As in the studies performed in SI and AI, one could expect that there would be a recruitment of cells toward the trained orientation. However, in contrast to the previous SI/AI studies, no comparable expansion in representation was found. Instead, the proportion of cells recorded in primary visual cortex (in monkeys trained to discriminate orientations) that preferred the orientation to which they had been trained, was not larger than the proportion of cells preferring any other orientation (Schoups, 2001). Parallel experiments using autoradiographic labelling of deoxyglucose as an indirect marker of neural activity (based on the close relation between oxygen consumption and firing activity) confirmed the electrophysiological data. No broadening of the orientation columns was observed as a consequence of the perceptual learning, and thus no recruitment occurred of cells responding to the trained orientation (Schoups, 2001). Moreover, outside the primary visual cortex no major and systematic changes have been found. Recordings in the inferotemporal cortex from rhesus monkeys trained to judge whether or not two successively presented gratings differed in orientation revealed no consistent effects either on the responsiveness or on the orientation tuning (Vogels and Orban, 1994).

More recent findings on the firing behaviour of neurones in striate cortex, recorded from monkeys trained in an orientation discrimination task, provided evidence for rather complex changes. In the population of trained neurones, those that preferred the trained orientation exhibited a lower firing rate than the neurones preferring other orientations (Schoups *et al*., 2000). At first sight this result seems counterintuitive. However, models of perceptual learning involving orientation discrimination (Qian and Matthews, 1999) predicted that lower firing rates by the neurones that prefer the trained orientation could lead to selective changes in the tuning patterns of neurones that prefer the orientations bordering the one trained, which then would lead to a better performance in the discrimination task. These results raise some interesting possibilities related to the coding of plastic changes (cf. also Dinse and Merzenich, 2002; Schoups, 2001), which will be discussed later (see also section 2.6. "Coding of plastic changes").

The paradigm of "modified use" as a determinant of cortical organization has been applied in a large number of investigations, mostly performed in somatosensory cortex (cf. Dinse and Merzenich, 2002), with few studies in other modalities. In this approach, plastic changes are analyzed in a rather natural context, where the link between behaviour and cortical reorganization is often less quantifiable, but still intuitively obvious. For example, the implications of episodes of differential use, following nursing behaviour, occurring during the normal life-span of an animal, have been shown in a study of lactating rats. The SI representation of the ventral trunk skin was significantly larger than in matched postpartum

non-lactating or virgin controls (Xerri *et al.*, 1994). After training squirrel monkeys on a task involving retrieval of small objects, which required skilled use of the digits, their motor digit representations expanded, whereas their evoked-movement wrist/forearm representational zones contracted. In a second task, a monkey was trained in a key-turning task. In this case, the representation of the forearm expanded, whereas the digit representational zones contracted. Movement combinations that were used more frequently after training were selectively magnified (Nudo *et al.*, 1996). Interestingly, repetitive motor activity alone appeared not to produce functional reorganization of cortical maps indicating that skill acquisition or motor learning is a prerequisite factor for induction (Plautz *et al.*, 2000; but see section 2.3.2. "Coactivation" on this issue).

In the auditory system, abnormal cochleotopic organization in the auditory cortex of cats reared in a frequency-augmented environment has been observed (Stanton and Harrison, 1996). For the visual system, Sugita (1996) reported that V1 neurones in monkeys can develop novel receptive fields to the ipsilateral hemifield after monkeys have worn reversing spectacles for several months. These studies suggest that visual cortical neurones can in fact acquire novel inputs, not only from neighbouring retinal areas, but also from distant nonadjacent areas. This report contradicts earlier findings, according to which the visual field representation in the striate cortex is rigidly prewired with reference to the anatomical fovea (cf. Pöppel *et al.*, 1987). It is well established that perceived orientation can be influenced by previous adaptation to a tilted stimulus (tilt aftereffect), an illusion that decays rapidly over time. Following short-term adaptation to one stimulus orientation, systematic "rebound" shifts in orientation preference were observed, that included changes in orientation tuning away from the adapting stimulus indicating the involvement of widespread network interactions that mediate these effects (Dragoi *et al.*, 2000).

The recent development of non-invasive imaging techniques has made it possible to study the impact of modified use and practice in humans. Imaging studies performed over the last few years provided overwhelming evidence that extensive use and practice result in substantial changes of associated cortical representations. For example, in the somatosensory cortex of blind Braille readers (Pascual-Leone and Torres, 1993; Sterr *et al.*, 1998a,b) and of string players (Elbert *et al.*, 1995), selective enlargement was found for those cortical territories representing the digits engaged in more extensive use, as exemplified by the reading fingers (Braille readers) or the fingering digits (string player). In adults who were studied before and after surgical separation of webbed fingers, a cortical reorganization of the finger representation over several millimeters was observed (Mogilner *et al.*, 1993), a finding reminiscent to what had been reported some years ago for artificial induction of syndactyly in monkeys (Clark *et al.*, 1988). Subjects engaged in long-term perceptual training in tactile discrimination revealed changes in responsivensss of the somatosensory cortex (Spengler *et al.*, 1997). When subjects received passive tactile stimulation of thumb and little finger over a period of 4 weeks, the representations of the fingers in primary somatosensory cortex were closer together after training. However, when subjects had to discriminate stimuli, MEG imaging revealed that the digital representations were further apart than before. Thus, the same prolonged repetitive stimulation produced two opposite effects, suggesting that activation in the same region of cortex is specific to different tasks (Braun *et al.*, 2000).

In order to demonstrate the perceptual relevance of the neural changes induced by a tactile coactivation protocol (see also section "2.3.2. Coactivation"), spatial discrimination performance was investigated in human subjects who underwent a similar passive coactivation,

as described in the animal study by Godde *et al.* (1996). A small skin area on the index finger was coactivated. Discrimination thresholds were used as a marker of reorganizational effects on human perception. It was found that two hours of coactivation were sufficient to drive a significant improvement of the spatial discrimination performance (Godde *et al.*, 2000), demonstrating the potential role of pure input statistics for the induction of cortical plasticity without involving cognitive factors such as attention or reinforcement. A combined assessment of discrimination thresholds and recording of somatosensory evoked potentials in human subjects revealed that the individual gain of discrimination performance was correlated with the amount of cortical reorganization, as inferred from the shifts of the location of the "N20" dipole (Pleger *et al.*, 2001).

For the human motor system, similar fast adaptational regulations have been reported: using mapping of responses to transcranial magnetic stimulation (TMS), in human subjects who had unilateral immobilization of the ankle joint (i.e. they had to wear a cast for a couple of weeks), the area of motor cortex representing the *tibialis anterior* muscle were significantly reduced compared to the representation of the unaffected leg. The amount of areal reduction was correlated with the duration of immobilization, an effect rapidly reversed by voluntary muscle contractions (Liepert *et al.*, 1995). An hour of synchronous movements of the thumb and foot resulted in a reduction of the distance of the centre of gravity of their respective output maps in the primary motor cortex, whereas asynchronous movements evoked no significant changes, indicating that similar principles of coactivation hold for both the sensory and motor system (Liepert *et al.*, 1999).

In highly skilled musicians, functional magnetic source imaging revealed an enlargement of dipole moments for piano tones, but not for pure tones of similar fundamental frequency, which was correlated with the age at which musicians began to practice (Pantev *et al.*, 1998). In addition, musicians with absolute pitch were characterized by distinct neural activities in the auditory cortex (Hirata *et al.*, 1999). Similarly, auditory cortical representations for tones of different timbre (violin and trumpet) were enhanced compared to sine tones in violinists and trumpeters, preferentially for timbres of the instrument of training (Pantev *et al.*, 2001). Reminiscent of the reorganizations after frequency-discrimination training in monkeys (Recanzone *et al.*, 1993), human subjects have been reported to show plastic reorganization in the auditory cortex induced by frequency-discrimination training over several weeks. Changes consisted of an increase of amplitude of the slow auditory evoked (wave "N1m") and mismatch field (Menning *et al.*, 2000).

The human visual system is able to determine very precisely the relative positions of objects in space. Using an artificial scotoma, by occluding part of the visual field, while a pattern was shown over a surrounding region, resulted in severe mislocalization. This was due to a strong bias toward the interior of the scotoma, indicating a significant short-term cortical plasticity in adult human vision (Kapadia *et al.*, 1994). In a psychophysical and functional imaging study of adaptation to inverting spectacles, subjects showed rapid adaptation of visuomotor functions within several days, but did not report return of upright vision. This was corroborated by the functional magnetic resonance images (fMRI) that failed to show alteration of the retinotopy of early visual cortical areas (Linden *et al.*, 1999), a finding in contrast to recent animal data demonstrating indeed a functional reversal in area 17 after months of training (Sugita, 1996). Transcranial magnetic stimulation (TMS) of the occipital cortex evokes the perception of phosphenes. In human subjects, a reduced phosphene threshold was detected 45 min after a short period of light deprivation, and this persisted for the whole deprivation period of 3 h. Similarly, fMRI showed increased visual

cortex activation after 60 min of light deprivation that persisted following 30 min of re-exposure to light, demonstrating a substantial increase in visual cortex excitability (Boroojerdi *et al.*, 2000). It was speculated that such changes may underlie behavioural gains such as a lowered visual recognition thresholds reported in humans associated with light deprivation (Suedfeld, 1975).

The tilt aftereffect leads to wide-spread changes of visual cortex orientation maps (Dragoi *et al.*, 2000). When alphanumeric characters were presented to human subjects with a clockwise tilt, they were perceived as less tilted than the same stimulus horizontally inverted. In contrast, subjective perception of tilt magnitude for horizontally inverted non-alphanumeric stimuli was similar to that for non-inverted stimuli reflecting a persistent sensory recalibration of orientation perception as a result of previous long-term visual experience (Whitaker and McGraw, 2000).

Taken together, these studies suggest that even small alterations in behaviour due to special demands imposed in everyday life alter early cortical representations rapidly and reversibly. The human studies summarized confirm the close relation between intensified or altered use (on the one hand) and enlargement of associated cortical representational maps (on the other hand), supporting the relevance of the concept of cortical plasticity for everyday life. From a comparative point of view, it appears fair to state that while there is a large body of information about use- and experience-related plastic changes in somatosensory and auditory cortex, comparatively little is known about visual cortex.

2.3. The Role of Input Statistics

Human studies of the type summarized are very helpful in revealing signatures of cortical plasticity under everyday life conditions. However, these studies are not designed to control precisely for input pattern. Accordingly, it remains unclear what are the "driving factors" leading to reorganization. In the case of the blind Braille readers, potential candidates are: the frequency of finger usage, the spatial pattern of the Braille signs, the spatio-temporal pattern arising when the finger is moved across the Braille signs, the level of attention, and the duration of practice. In addition, many lines of evidence have shown that cortical systems adapt to input patterns characterized by different probabilities, implying that variations of input statistics alone are sufficient to induce reorganization of cortical maps, i.e. without involving cognitive processes such as those present in training protocols. Therefore, animal studies are required that complement and extend human studies by a systematic variation of input pattern.

2.3.1. Intracortical microstimulation

Intracortical microstimulation (ICMS) is used to evoke selective motor responses by applying current through microelectrodes inserted into defined regions of motor representations. More recently, this technique has been utilized to study short-term and reversible plastic changes in various cortical regions, including motor (Nudo *et al.*, 1990; Gu and Fortier, 1996; Kimura *et al.*, 1996), somatosensory (Dinse *et al.*, 1990; Recanzone *et al.*, 1992d; Dinse *et al.*, 1993; Spengler and Dinse, 1994; Joublin *et al.*, 1996; Xing and Gerstein, 1996; Dinse *et al.*, 1997a; Heusler *et al.*, 2000), auditory (Sil'kis and Rapoport, 1995; Maldonado and Gerstein, 1996a,b; Maldonado *et al.*, 1998; Sakai and Suga, 2001) and visual (Leonhardt *et al.*, 1997; Godde *et al.*, 2002) cortices, as well as thalamic relay nuclei of the somatosensory system (Dinse *et al.*, 1997a).

A specific advantage of ICMS is that it allows one to investigate locally the properties of functional plasticity, independent of the peripheral and subcortical pathways and independent of the constraints provided by particularities of a sensory pathway and its preprocessing. In a typical ICMS experiment, repetitive electrical pulse trains of very low currents (usually less than 10 μA) are delivered via a microelectrode. Based on theoretical calculations, ICMS of that intensity activates a cortical volume of only 50 microns in diameter (Stoney *et al*., 1968). The resulting synchronized discharges are assumed to be crucial for mediating plastic changes. The short time scale and reversibility of ICMS-induced effects support the hypothesis that modulations of synaptic efficiency in neuronal networks can occur very rapidly without necessarily involving anatomical changes. Consequently, ICMS is an ideal method for studying possible modality- and area-specific constraints of cortical plasticity.

In the rat motor cortex, significant changes in representations of movement were observed after a few hours of ICMS, these being fully reversible. Changes were characterized by border shifts up to more than 500 microns (Nudo *et al*., 1990). Application of ICMS in the hindpaw representation of the adult rat somatosensory cortex caused an overall but selective expansion of receptive field size up to 1 mm around the ICMS site (Recanzone *et al*., 1992d; Dinse *et al*., 1993; Spengler and Dinse, 1994). Receptive fields close to the stimulation site were enlarged, and comprised large skin territories, always including the receptive field at the ICMS-site, revealing a distance-dependent, directed enlargement towards the ICMS-receptive field. Early ICMS-related reorganization could already be detected after 15 min of ICMS, and much greater effects emerged after 2 to 3 hours, which were reversible within 6 to 8 hours after termination of ICMS (Dinse *et al*., 1993; Spengler and Dinse, 1994).

In the auditory cortex, ICMS induced fast changes in the tonotopic map, and in the receptive field properties of cells at the electrically stimulated and adjacent electrodes. There was an enlargement of the cortical domain tuned to the acoustic frequency that had been represented at the stimulating electrode (Maldonado and Gerstein, 1996a,b; Maldonado *et al*., 1998). Comparison of reorganization evoked by focal electric stimulation (ICMS) in AI of an ecologically highly specialized animal (the mustached bat—*Pteronotus parnellii*) and a non-specialized one (the Mongolian gerbil—*Meriones unguiculatus*) revealed differences in the ICMS-induced shifts of best frequency, implying differences between specialized and nonspecialized (ordinary) areas of the auditory cortex (Sakai and Suga, 2001).

ICMS-induced reorganization in somatosensory and visual cortex of pigmented rats was compared in individual animals (Leonhardt *et al*., 1997, 1998). In visual cortex, ICMS led to small (~20%), but significant expansions of receptive fields for a subpopulation of neurones with small receptive fields pre-ICMS. Neurones characterized by initially large RFs did not change. In contrast, RFs recorded in SI in the same animal, exhibited the well-known several-fold enlargement. In addition, in visual cortex, the time-structure of the neuronal responses was systematically altered, by suppressing late response components, leading to profound changes in the temporal structure of the receptive field dynamics. Comparable changes have not been observed in SI. As a further difference, in visual cortex, the observed changes were not reversible within the observation period of 3–6 h after ICMS.

To further investigate the plasticity of functional maps in the visual cortex, orientation-preference maps were recorded by means of optical imaging. A few hours of ICMS induced major changes of orientation-preference maps in adult cats (Godde *et al*., 1999, 2002). These results showed that orientation-preference maps undergo substantial expansions

reminiscent of non-visual cortical maps. However, changes were much more wide-spread and enduring, indicating that the large-scale changes of the functional architecture resulted from a restructuring of the entire underlying cortical network. Parallel electrophysiological single cell recordings revealed distinct shifts of the individual orientation tuning towards the preferred orientation present at the ICMS site. Again, no changes of receptive field sizes were found.

Taken together, these results from ICMS experiments imply that sensory cortex, including visual cortex, is modifiable in adults, both in terms of functional maps and in terms of single cell properties. However, there appear to exist a number of differences, best documented for somatosensory and visual cortex, concerning reversibility, spatial range of changes, and neural response parameters most susceptible to modifications.

2.3.2. Coactivation

A number of protocols have been introduced in which neural activity, necessary to drive plastic changes, was generated by an associative pairing protocol. In the pioneering studies by Fregnac and coworkers (Fregnac *et al.*, 1988, 1992), persistent functional changes in response properties of single neurones of cat visual cortex were induced by a differential pairing procedure, during which iontophoresis was used to increase artificially the visual response for a given stimulus, and to decrease the response for a second stimulus. Neuronal selectivity was nearly always displaced towards the stimulus paired with the reinforced visual response, thereby leading to long-term modifications of orientation selectivity in about one third of the neurones tested. The largest changes were obtained at the peak of the critical period in normally reared and visually deprived kittens, but changes were also observed in adults. From a conceptual point of view, these findings supported the role of temporal correlation between pre- and postsynaptic activity in the induction of long-lasting modifications of synaptic transmission in associative learning during development and in adults.

A similar modifiability of response properties of visual cortex neurones in adult cats has been observed after a conditioning protocol, where the presentation of particular visual stimuli was repeatedly paired with the iontophoretic application of either GABA or glutamate to control postsynaptic firing rates (McLean and Palmer, 1998). The modification in orientation tuning was not accompanied by a shift in preferred orientation, but rather, responsiveness to stimuli at or near the positively-reinforced orientation was increased relative to controls, and responsiveness to stimuli at or near the negatively-reinforced orientation was decreased. These studies are in contrast to a previous study, where lasting (maximal 1 h) modifications of the receptive fields of neurones in the visual cortex were observed by pairing visual stimuli with iontophoretic application of the neuromodulators acetylcholine and noradrenaline or the excitatory amino acids N-methyl-D-aspartate (NMDA) and L-glutamate in kitten, but not in adult animals (Greuel *et al.*, 1988).

While these experiments emphasize the potential capacities of adult visual cortex for change of its response properties, it remains an interesting question, why comparable experiments (drug-pairing) have been performed in the other modalities very rarely (Maalouf *et al.*, 1998; Shulz *et al.*, 2000). Possibly, induction of plastic changes in adult visual cortex might be more "difficult" to drive than in other areas using more natural types of stimulation, without direct drug application (see also below). However, independent of this speculation, the present findings from drug-pairing experiments point to a rather common form of modifiability across cortical areas.

In contrast to the cellular pairing protocols, a number of studies utilized a pairing of adequate (i.e. sensory) stimuli, for the somatosensory cortex (Diamond *et al*., 1993; Wang *et al*., 1995; Godde *et al*., 1996, 2000) and visual cortex (Eysel *et al*., 1998). In the study by Diamond *et al*. (1993) sensory experience was altered by a few days of "whisker pairing": whiskers D2 and either D1 or D3 were left intact, while all other whiskers were trimmed. During whisker pairing, the receptive fields of cells in barrel D2 changed in distinct ways: the response to the centre receptive field increased, the response to the paired surround receptive field nearly doubled, and the response to all clipped, unpaired surround receptive fields decreased. These findings indicate that a brief change in the pattern of sensory activity induced by pairing of tactile stimuli can alter the configuration of cortical receptive fields of adult animals.

To test the hypothesis that consistently non-coincident inputs may be actively segregated from one another in their distributed cortical representations, monkeys were trained to respond to specific stimulus sequence events (Wang *et al*., 1995). Animals received temporally-coincident inputs across fingertips and fingerbases, but distal *vs* proximal digit segments were non-coincidentally stimulated. Electrophysiological recordings in somatosensory cortex (area 3b) showed that synchronously applied stimuli resulted in integration of inputs in the cortical maps, whereas stimuli applied asynchronously were segregated by two band-like zones, in which all neurones had multiple digit receptive fields representing the stimulated skin surfaces. Interestingly, maps derived in the ventroposterior portion of the thalamus were not reorganized in an equivalent way, suggesting that this particular type of representational plasticity appears to be cortical in origin.

In the study by Godde *et al*. (1996), receptive fields on the hindpaw of adult rats were used for coactivation. These authors reported reversible reorganization consisting of a selective enlargement of the cortical territory, and of the receptive fields representing the co-stimulated skin fields. In addition, a large representation emerged that included a joint representation of both skin sites. A control protocol applied to only a single skin site evoked no changes indicating that coactivation was essential for induction (see also "2.2. Training and learning induced reorganization").

It has been stressed that passive stimulation, or repetitive motor activity alone appeared not to produce comparable functional reorganization of cortical maps (Recanzone *et al*., 1992b; Plautz *et al*., 2000). On the other hand, the coactivation studies reported here showed a clear effect on cortical as well as on perceptual levels, in spite of the fact that attention was not involved. One explanation is that during the coactivation protocol, which was on average applied at a rate of 1 Hz for several hours, selected skin regions were stimulated 10 000 times or more. This is a much stronger stimulation in terms of stimulus number per time than the monkeys received during the passive discrimination training. Conceivably, the intensity of the stimulation/movement protocol might be the crucial factor responsible for its effectiveness.

For the visual system, early studies claimed that retinal stimulation alone does not induce plastic changes (Buisseret *et al*., 1978). However, a recent coactivation study, performed in mature visual cortex, revealed the capacity for significant changes of receptive field organization: single cortical cells expanded their receptive fields, within minutes, into previously-unresponsive regions, and changed their functional receptive field structure for hours after associative co-stimulation of active and primarily-unresponsive regions (Eysel *et al*., 1998). While this study corroborates the sensitivity of visual cortex to a coactivation protocol consisting of natural sensory stimuli, the magnitude of changes are clearly below

those reported for SI. However, given the many differences in methodological details, more experiments are required to provide a final answer about possible underlying modality-specific differences.

2.3.3. Classical conditioning

Another type of associative learning, as exemplified by classical conditioning, has been studied for decades, in several variations, in the auditory cortex (for review see Weinberger *et al*., 1990; Weinberger, 1995). Using a classical conditioning protocol, a tone of a given frequency (as the CS+) was paired with an aversive electrical shock. Tuning curves recorded in the auditory cortex before and after conditioning revealed a shift in the best frequencies in the direction of the frequency of the CS+; these shifts lasted up to a few weeks and could be reversed by extinction training (Diamond and Weinberger, 1986: Bakin and Weinberger, 1990; Edeline and Weinberger, 1993; Ohl and Scheich, 1996). Most conspicuously, the approach of classical conditioning to studying aspects of cortical plasticity appears to be entirely restricted to studies of the auditory system, ruling out any comparative analysis, although the restriction to the auditory system might, in itself, hint at some particular modality-specific constraints that might be worth exploring in more detail. Anecdotally, classical conditioning was discovered by Durup and Fessard in the visual cortex of humans many decades ago (cited by Weinberger *et al*., 1990). However, this was conditioning of the alpha rhythm, and may have involved conditioning of subcortical control mechanisms, rather than at the cortical level. Such conditioning, is likely to be important, but is not the focus of the present chapter.

2.4. Pharmacological Modulation of Adult Plasticity

There are many sources modulating cortical responsiveness and plasticity. The major source of cholinergic inputs that have long been implicated in learning and memory comes from several groups of neurones within the basal forebrain, which receives inputs from limbic and paralimbic structures. These inputs have been assumed to represent one example of a top-down system providing modulatory information of higher-order—presumably cognitive—processes. For example, in animal experiments, pairing of sensory stimulation with electrical stimulation of the *nucleus basalis* has been shown to result in rapid and selective reorganization (in the somatosensory cortex by Rasmusson and Dykes [1988], in the auditory cortex by Edeline *et al*. [1994], Bakin and Weinberger [1996], Bjordahl *et al*. [1998] and by Kilgard and Merzenich [1998a]). On the other hand, lesions of the cholinergic system have been shown to prevent plastic reorganization in the somatosensory cortex (Baskerville *et al*., 1997; Sachdev *et al*., 1998). However, using a whisker pairing protocol, in which all but a few whiskers were trimmed, the animal's active use of its remaining intact whiskers can restore some aspects of plasticity in an acetylcholine-depleted cortex (Sachdev *et al*., 2000). Direct administration of acetylcholine (ACh) to cortical neurones facilitates or suppresses responses to sensory stimuli, and these effects can endure well beyond the period of ACh application. In primary auditory cortex, analysis of single neurone frequency receptive fields, before and after such pairing of acoustic stimulation with ACh application revealed that in half of the cases, the receptive field alterations were highly specific to the frequency of the tone previously paired with ACh (Metherate and Weinberger, 1990). The involvement of neuromodulatory effects in cortical Hebbian-like

plasticity of acetylcholine (ACh) and noradrenaline (NE) was related to the timing of drug applications, relative to the conditioning time, their local concentrations and/or the site of application with respect to the relevant synapses (Ahissar *et al.*, 1996).

Ocular dominance plasticity is strongly expressed in early postnatal life and is usually assumed to be absent in the mature visual cortex. Local perfusion of kitten visual cortex with 6-hydroxydopamine (6-OHDA) prevented the effects of monocular deprivation in kittens, while locally perfused norepinephrine restored visual cortical ocular dominance plasticity (Kasamatsu *et al.*, 1979). The effect of norepinephrine perfusion was seen both in kittens and, though to a lesser degree, in older animals which had outgrown the susceptible period. More recently, it was demonstrated that activation of cAMP-dependent protein kinase A could restore ocular dominance plasticity in visual cortex of adult cats (Imamura *et al.*, 1999). These findings indicate that various forms of visual cortex organization can be affected, and persistently modified in adults. More generally, the former data are in line with the well-documented catecholaminergic and cholinergic modulation of post-ontogenetic cortical plasticity well established for auditory and somatosensory cortex.

2.5. Therapeutic Consequences of Cortical Plasticity

The final outcome of reorganizational processes must not necessarily be beneficial. There is increasing evidence that abnormal perceptual experiences, such as the phantom limb sensation, arise from reorganizational changes induced by the amputation of the limb (Flor *et al.*, 1995, 1998). In amputees, a number of perceptual correlates of cortical reorganizations have been described, such as a precise topographic mapping of the phantom onto the face area, these being explained on the basis of the topography of the border of the face-hand maps (Ramachandran *et al.*, 1992; Halligan *et al.*, 1993; Aglioti *et al.*, 1997). In patients with chronic pain, the power of the early evoked magnetic field, elicited by painful stimulation, was elevated relative to that elicited by the same stimulation in healthy controls. Furthermore, this enlargement was a function of the chronicity of pain (Flor *et al.*, 1997). Repetitive strain injuries, such as focal dystonia, have a high prevalence in workers who perform heavy schedules of rapid alternating movements, or repetitive, sustained, coordinated movements. It has been hypothesized that use-dependent plastic changes, as reviewed in this chapter, may cause these injuries (Byl *et al.*, 1996, 1997). Monkeys trained in repetitive hand closing and opening developed typical signs of movement control disorders. Electrophysiological recordings within the primary somatosensory cortex revealed a de-differentiation of cortical representations of the skin of the trained hand, manifested by receptive fields that were 10 to 20 times larger than normal (Byl *et al.*, 1996). A recent study using MEG in musicians suffering from focal hand dystonia revealed a smaller distance between the representations of the affected digits in somatosensory cortex, compared to the same digits in non-musician controls (Elbert *et al.*, 1998) indicating similar neural changes in humans as a consequence of repetitive strain injuries.

The negative outcome of neuroplasticity may also play a major role in some forms of age-related changes. It has been suggested that reorganizational processes lead to maladaptive changes, as a result of walking impairments, developed in rats of high age as a secondary response to muscle atrophy and other factors promoting limited agility (Spengler *et al.*, 1995; Jürgens and Dinse, 1997a; Dinse and Merzenich, 2002; Dinse, 2001).

In the auditory domain, some forms of dysfunctions in normal phonological processing, which are critical to the development of oral and written language, have been speculated

to derive from initial difficulties in perceiving and producing basic sensory-motor information in rapid succession, emphasizing the crucial role of temporal parameters. In fact, when children with a particular type of language-based learning deficit were engaged in adaptive training of their temporal processing skills, they showed a marked improvement in their abilities to recognize brief and fast sequences of non-speech and speech stimuli. This suggests that the reorganizational changes are specifically sensitive to temporal parameters of the input (Tallal *et al*., 1993, 1996; Merzenich *et al*., 1996).

People with amputations often have the feeling that the amputated limb is still present (phantom limb sensation). Subjective tinnitus, the hearing of a disturbing tone or noise in the absence of a real sound source, shares many similarities with the sensation of phantom limb, experienced by many amputees. Therefore, tinnitus has been thought of as an auditory phantom phenomenon (Jastreboff, 1990; Lockwood *et al*., 1998; Rauschecker, 1999). A marked shift of the cortical representation of the tinnitus frequency into an area adjacent to the expected tonotopic location was observed in subjects suffering from tinnitus. Importantly, a strong positive correlation was found between the subjective strength of the tinnitus and the amount of cortical reorganization (Mühlnickel *et al*., 1998), indicating that tinnitus is related to plastic alterations in auditory cortex. Studies using 2-deoxyglucose autoradiography in gerbils treated with salicylate (known to generate tinnitus) demonstrated increased activation in areas of the auditory cortex (Wallhäusser-Franke *et al*., 1996).

Cochlear implants (CI) are a frequent measure to provide sound perception in patients with sensorineural hearing loss. Utilizing the critical period for speech acquisition, clinical data suggest that children implanted before 2 years of age have an excellent chance of acquiring speech understanding. For implanted children, maturational delays for cortically-evoked potentials, that approximated the period of auditory deprivation prior to implantation, were reported (Ponton *et al*., 1996). In cats implanted with multichannel intracochlear electrodes, long-term electrical CI stimulation was found to induce substantial reorganization of cortical auditory maps, consisting of a selective enlargement of that territory representing the frequency representations stimulated during chronic CI (Dinse *et al*., 1997b). It was suggested that the outcome of these reorganizations was due to Hebbian mechanisms, utilizing the simultaneity induced by the CI stimulation strategy (continuous interleaved sampler) in which at high stimulation rates all frequency channels are stimulated virtually simultaneously (viz within a single millisecond). Notably, the CIS strategy has proven highly effective in human patients in providing a high level of open speech understanding (Wilson *et al*., 1991). Similar reorganizational changes were observed in cats deafened and chronically CI-stimulated as adults (Dinse *et al*., 1997b, 1998; Godde *et al*., 1998). Major differences in cortical response distributions on the ectosylvian gyrus of adult cats due to deafening were also observed in long-term deafened animals. The authors speculated that these changes may reflect electrode-specific effects or reorganizational changes, as a consequence of the altered inputs (Raggio and Schreiner, 1999).

Recent imaging data obtained using positron emission tomography (PET), in prelingually deaf patients before and after cochlear implantation support the relevance of these animal findings for human patients (Lee *et al*., 2000). After cochlear implantation, these authors found a positive correlation between the size of the hypometabolic area and a hearing-capability score. Accordingly, several lines of evidence indicate that the underlying plastic adaptational properties of cortical auditory neurones might provide the substrate involved in mediating the highly variable improvement of open speech understanding with practice, often observed in patients with hearing aids.

That adult visual cortex is indeed also capable of long-term changes, induced by simple training procedures, comes from recent studies in which partially blind subjects obtained some restitution of their visual field (Kasten *et al*., 1998). In visual restitution training, visual stimuli were presented on a computer screen in such a manner that the majority of stimuli appeared in the transition zone, which is usually located in the border region between the intact and damaged visual-field, as well as near the border of the transition zone and the defective field. When post-chiasma patients were trained for 6 months, (1 h per day), subjects showed a 30% improvement in the ability to detect visual stimuli. In optic nerve patients, the effects were even more pronounced. While in the past, partial blindness after brain injury has been considered non-treatable, these data are in line with a profound capacity of the visual cortex to reorganize, even in adults.

Of particular interest are findings on cross-modal plasticity in blind subjects, this contributing to sensory compensation when vision is lost early in life (Cohen *et al*., 1997; Weeks *et al*., 2000, for a general account of cross-modal plasticity; see also Pallas, this volume). To identify differences in cross-modal reorganization, depending on the time of onset of blindness, and thereby distinguishing effects due to ontogenetic or post-ontogenetic plastic processes, blind subjects were studied by means of positron emission tomography, to identify cerebral regions activated in association with Braille reading. In the congenitally blind and early-onset blind groups, the occipital cortex was strongly activated, but this did not occur in the late-onset blind group. These results indicate that the susceptible period for this form of functionally relevant cross-modal plasticity does not extend beyond 14 years (Cohen *et al*., 1999). To determine whether the visual cortex receives input from the somatosensory system during a Braille reading task, positron emission tomography (PET) was used to measure activation in Braille readers blinded in early life. Blind subjects showed activation of primary and secondary visual cortical areas during tactile tasks, whereas normal controls showed deactivation. Importantly, a simple tactile stimulus that did not require discrimination produced no activation of visual areas (Sadato *et al*., 1996). Comparing behavioural and electrophysiological markers of spatial tuning within central and peripheral auditory space in congenitally blind and normally sighted but blindfolded adults, the hypothesis was tested that the effects of visual deprivation might be more pronounced for processing peripheral sounds. In fact, blind participants displayed localization abilities that were superior to those of sighted controls, but only when attending to sounds in peripheral auditory space. Electrophysiological recordings obtained at the same time revealed sharper tuning of early spatial attention mechanisms in the blind subjects. Differences in the scalp distribution of brain electrical activity between the two groups suggest compensatory reorganization in the blind, which may contribute to the improved spatial resolution for peripheral sound sources (Röder *et al*., 1999).

Taken together, the maladaptive consequences of cortical plasticity are more and more acknowledged as a major factor in various forms of dysfunctions, an assumption apparently valid across modalities.

2.6. Coding of Plastic Changes

How are plastic changes coded? What neural response parameters are affected by the various forms of manipulations leading to reorganizations, and the parallel changes of perception and behavior? The studies discussed so far have in common that they almost exclusively describe reorganizational changes in terms of receptive field size and in size of cortical

representational territory. Particularly, the new imaging techniques such as fMRI allow one to study adaptational changes in humans, describing neural representations in terms of activation size of cortical maps. At least one simple rule-of-thumb appears to hold: extensive use leads to enlarged cortical territories, while limited use or no-use results in a reduction of cortical representational size, indicating a form of proportionality between representational area and use. Representational size correlates with the number of neurones activated by a given task or stimulation. This view implies that enhanced performance is at least partially achieved by recruitment of processing resources. However, a recent animal study suggested that exceptions might exist (Polley *et al.*, 1999b): allowing an animal to use its deprived receptor organ in active exploration appeared to determine the direction of plastic changes in the adult cortex. Further studies are needed to explore whether a similar potential for a use-dependent direction of reorganizational changes holds true in normal, nondeprived animals. From a more general point of view, this study suggests that the outcome of plastic processes might depend on far more subtle constraints imposed by the individual task than previously thought. In fact, as discussed for the visual cortex, a simple recruitment after perceptual learning of orientation discrimination could not be demonstrated (see also section 2.2. "Training and learning induced reorganization").

More recently, temporal aspects of processing, i.e. aspects of coding in the time domain, have been recognized as an additional and highly significant candidate code. As a consequence, aspects of synchronicity and correlated activity have been intensively studied, revealing that cooperativity among many neurones is indeed subject to profound modification during plastic reorganization. (This has been shown in the somatosensory cortex by Dinse *et al.* [1990, 1993]; Faggin *et al.* [1997] and by Ghazanfar *et al.* [2000], in the auditory cortex by Ahissar *et al.* [1992, 1998] and Maldonado *et al.* [1996a,b] and in the motor cortex by Laubach *et al.* [2000]).

These findings imply that changes in temporal coding are crucial for our understanding of use-dependent plasticity. Accordingly, a critical step for the investigation of how distributed cell assemblies process behaviourally-relevant information is therefore the introduction of methods for data analysis that can identify functional neuronal interactions within high-dimensional data sets (cf. Nicolelis, 1999). Laubach *et al.* (2000) applied such methods by chronically recording from neuronal ensembles located in the rat motor cortex. Based on such an elaborate approach they could demonstrate that motor learning was correlated with an increase in the experimenter's ability to predict a correct or incorrect single trial, based on measures of neuronal ensemble activity such as firing rate, temporal patterns of firing, and correlated firing.

On the other hand, temporal processing, i.e. the computation of sequential events, which is particularly important in the auditory system, is still poorly understood. Under natural conditions, stimuli never appear in isolation. Therefore, timing and sequencing impose severe temporal constraints that modulate neurone responses (Zucker, 1989; Chance *et al.*, 1998). There is, in fact, clear experimental evidence that repetitively applied stimuli alter the cortical response behaviour, as compared to a single stimulus (Gardner and Costanzo 1980; Lee and Whitsel, 1992; Dinse, 1994; Merzenich *et al.*, 1993; Tommerdahl *et al.*, 1998; Polley *et al.*, 1999a). So far, only a few studies have explored how far temporal processing is affected and altered by plastic reorganizations. For example, as described above, Recanzone *et al.* (1992c) demonstrated that behavioural training of a frequency-discrimination task affected entrainment of repetitive stimuli in the somatosensory cortex. To test whether experience can modify the maximum rate of following in adult rats, trains

of brief tones with random carrier frequency, but fixed repetition rate, were paired with electrical stimulation of the *nucleus basalis.* This was continued 300–400 times per day for 20–25 days. Pairing *nucleus basalis* stimulation with 5-p.p.s. stimuli markedly decreased the cortical response to rapidly presented stimuli, whereas pairing with 15-p.p.s. stimuli significantly increased the maximum cortical following rate, indicating an extensive cortical remodeling of temporal response properties (Kilgard and Merzenich, 1998b).

In the studies on age-related changes of the hindpaw representation in old rats, the neural response behaviour following repetitive stimulation was studied with trains of tactile stimuli of variable interstimulus intervals (ISIs). Dramatic impairment of repetition coding and input sequence representations were observed in old rats as compared to young controls (Jürgens and Dinse, 1995), and comparable changes of the neural input sequence representation were found in rats with artificially induced walking alterations (Jürgens and Dinse, 1997b). As discussed in the next main section of this chapter, there is an extensive literature about changes of temporal aspects in *in-vitro* studies.

Taken together, neural changes as a consequence of adaptational mechanisms include a large number of both spatial and temporal parameters of sensory processing. However, even under normal conditions, i.e. without involving adaptive processes, we have a poor understanding of both sensory processing and how performance is coded. That is why it is not clear what is meant by receptive field size. Is it "good" when a tuning curve gets sharper? "Good" for what? As exemplified by the study of Schoups *et al.* (2000), perceptual learning can be accompanied by rather unexpected changes: those neurones that preferred the trained orientation exhibited a lower firing rate than the neurones preferring other orientations. Conceivably, an apparent lack of plastic capacities might simply reflect hidden changes in parameter regimens presently not recognized or understood.

2.7. Is There an Area-specificity of Particular Cortical Visual Cortex Plasticity?

Though not representative, inspection of the quantity of publications as provided by Medline offers some insight into areas regarded important and accessible for scientific explorations. Comparing papers published in the field of somatosensory and visual plasticity revealed a number of interesting differences. When normalized to the absolute number of published papers in both fields, the same percentage (about 5%) were devoted to the exploration of "plasticity". Searching among these papers for "developmental plasticity" revealed 18% for visual, but only 5%" for somatosensory cortex, a discrepancy already noted by Weinberger (1995). "LTP" plus "NMDA" were found in 17% of visual cortex papers, but only in 6% dealing with somatosensory cortex. On the other hand, "adult reorganization" showed up in 4% of visual, but in 24% of somatosensory cortex studies. Similarly, "adult plasticity of cortical maps and receptive fields" was found in 8% of visual, but in 24% of somatosensory cortex papers. Finally, "perceptual learning" revealed 0.5% in the visual, but only 0.1% in the tactile modality. Combined, even if treated with ample caution, these data imply the existence of some particular differences between these areas concerning plastic changes.

These particularities are reflected in the discrepancy that, as shown above, training and learning induce powerful cortical reorganizations, but most of what we know about cortical plasticity in adults comes from experiments in somatosensory or auditory cortex. However, as summarized in the next section, *in-vitro* studies using slice preparations demonstrate very convincingly the existence of the whole spectrum of cellular mechanisms

in adult visual cortex crucial for mediating synaptic plasticity. Moreover, recent findings on perceptual learning in the visual and other domains imply the modifiability of adult visual cortex.

Although cortical maps are widely believed to emerge in the developing brain by activity-dependent mechanisms, the apparent stability of the basic layout of orientation preference maps of visual cortex has raised the suspicion that orientation-preference maps may be governed not only by activity-dependent processes, but may even be pre-specified intrinsically (Blakemore, 1977; Sengpiel *et al*., 1998; Miller *et al*., 1999). In the visual cortex, the precise match of orientation is a prerequisite for stereoscopic vision. Whether visual experience is responsible for the match was tested in a reverse-suturing experiment, in which kittens were raised so that both eyes were never able to see at the same time. A comparison of the layout of the two maps formed under these conditions showed them to be virtually identical. Considering that the two eyes never had common visual experience, this indicates that correlated visual input is not required for the alignment of orientation preference maps (Gödecke and Bonhoeffer, 1996). It was therefore suggested that the geometry of functional maps in the visual cortex might be intrinsically determined, while the relative strength of representation of different response properties can be modified through visual experience (Sengpiel *et al*., 1998). On the other hand, kittens reared in a striped environment responded to all orientations, but devoted up to twice as much cortical area to the experienced orientation as to the orthogonal one. This effect has been attributed to the instructive role of visual experience whereby some neurones shift their orientation preferences toward the experienced orientation. Thus, although cortical orientation maps are remarkably rigid, in the sense that orientations that have never been seen by the animal are still represented and occupy a large portion of the cortical territory, visual experience can nevertheless alter neuronal responses to oriented contours (Sengpiel *et al*., 1999).

While these latter data refer to the critical sensitive period, there have been a number of studies many years ago that reported a substantial capacity of the adult visual cortex to reorganize. Creutzfeldt and coworkers reported that adult cats exposed to a visual environment consisting only of vertical stripes showed clear signs of plastic changes. The number of neurones sensitive to the vertical orientations relative to those sensitive to horizontal was markedly decreased (Creutzfeldt and Heggelund, 1975). In a previous study, Spinelli and coworkers analyzed response properties of visual cortical neurones in kittens which had viewed (from birth) horizontal lines with one eye and vertical lines with the other eye. Neurones with horizontal preferred orientations could be activated only by the eye exposed to horizontal lines, the analogous result was found for the vertical line. There was a consistent lack of binocularity (Hirsch and Spinelli, 1970). In a continuing study, these animals were re-exposed to a normal environment after about 2 months, for up to 19 months. After that period, the animals regained a high, but variable amount of binocularity (Spinelli *et al*., 1972) indicating that plastic capacities of visual cortical units extend well into adulthood (see their paper for an extensive discussion).

Taking the above results together, there appears at present to be a lack of striking readiness for adult visual cortex to reorganize as reported for the other modalities. Just how far these differences reflect a genuine area-specificity, or the outcome of the experimenters' belief that the adult visual system displays a higher degree of rigidity, remains a matter of debate. At any rate, evidence is accumulating that the adult visual cortex can be modified as well, although the parameters affected, and the modes of induction of plastic changes may be different.

3. CELLULAR MECHANISMS INVOLVED IN CORTICAL PLASTICITY

As far as neuronal mechanisms possibly involved in cortical plasticity are concerned, Hebbian synapses are thought to play an important role not only in cortical development in young animals, but also in cortical reorganization in adult animals (Buonomano and Merzenich, 1998). In the Hebbian rule (Hebb, 1949) a synaptic input to a neurone is strengthened when it repeatedly or persistently causes the postsynaptic neurone to discharge. Thus, the examination of cellular mechanisms involved in neuronal plasticity is mainly focused on the alteration of synaptic efficacy by adequate stimulation of axonal inputs to small populations of neurones, or to single pyramidal cells.

3.1. Synaptic Plasticity: The Hippocampus

Several forms of activity-dependent alteration of synaptic efficacy have been established since the first demonstration of long-lasting potentiation (LTP) of synaptic transmission from axons of the perforant path to neurones in the dentate gyrus of the hippocampus (Bliss and Lømo, 1973). In this study LTP was induced by tetanic stimulation *in vivo*. Subsequently, most studies on mechanisms involved in the induction of hippocampal synaptic plasticity were performed on brain slices. High-frequency stimulation (HFS; e.g. 1 sec at 100 Hz) of the Schaffer collaterals of CA3 pyramidal cells results in LTP of EPSPs recorded from pyramidal cells of the CA1 subfield, lasting at least 30 min and in most cases up to several hours. This form of synaptic plasticity of the hippocampus has been intensively studied (for reviews see Bliss and Collingridge, 1993; Malenka and Nicoll, 1993). Short-lasting forms of enhancement of synaptic strength (for review see Zucker, 1989) include short-term potentiation (STP) lasting up to 30 min, post-tetanic potentiation (PTP) lasting 30–40 s (Malenka and Nicoll, 1993) and paired-pulse facilitation lasting less than a second (PPF; Debanne *et al*., 1996). In contrast to HFS inducing LTP, low-frequency stimulation (LFS; e.g. 900 pulses at 1 Hz) of Schaffer-collaterals results in long-term depression (LTD) of EPSPs in CA1 pyramidal cells, i.e. in a sustained reduction of the synaptic efficacy (for review see Bear and Abraham, 1996). In some experimental protocols, synaptic depression of less than 30 min, or even less than a second, was observed. In analogy with STP and PPF, these forms of transient depression were termed STD (Artola and Singer, 1993) and PPD (Debanne *et al*., 1996), respectively. However, the term STD covers a variety of physiological processes including postsynaptic mechanisms, e.g. desensitization of neurotransmitter receptors, and presynaptic reduction of transmitter release from readily releasable stores (for review see Zucker, 1989). The latter is also true for PPD.

With some remarkable exceptions (for review see Johnston *et al*., 1992), LTP as well as LTD depend on activation of the NMDA type of glutamate receptor as indicated by the blocking action of NMDA receptor antagonists applied during conditioning stimulation (Collingridge *et al*., 1983; Mulkey and Malenka, 1992). In addition, the induction of either LTP or LTD was demonstrated to depend on the intracellular concentration of calcium (Mulkey and Malenka, 1992). According to the results of this study, LTD is induced by a moderate increase of the intracellular calcium concentration, while a strong increase of the intracellular calcium concentration results in the induction of LTP. Furthermore, intracellular studies revealed that the induction of either LTP or LTD strongly depends on the time-relation between presynaptic and postsynaptic activities (for review see Bliss and Collingridge, 1993, and the following section).

3.2. Synaptic Plasticity: The Adult Neocortex

There is some evidence that the first and primary site of synaptic modification involved in the reorganization of cortical maps is in the cortex (for review Buonomano and Merzenich, 1998). Thus, the focus of the present short review is on synaptic plasticity induced within the cortex. In a study examining the susceptibility of the neocortex to the induction of synaptic plasticity, compared to that in CA1 of the hippocampus, it was demonstrated that—depending on the stimulation frequency—conditioning stimulation in cortical layer IV induced either LTP (with HFS) or LTD (with LFS) in layer III of the adult rat visual cortex (Kirkwood *et al.*, 1993). Thus, common forms of synaptic plasticity can be induced in the hippocampus and the neocortex. However, the amount of enhancement in neocortical LTP is smaller and develops more slowly than in hippocampal LTP (Malenka, 1995). The features of synaptic plasticity of neocortical neurones have been studied most frequently in the primary visual cortex (Artola and Singer, 1987; Aroniadou and Teyler, 1991; Kirkwood and Bear, 1994a,b; Bear, 1996), but also in the primary and secondary somatosensory cortices (Castro-Alamancos *et al.*, 1995; Kitagawa *et al.*, 1997; Feldman, 2000; Heusler *et al.*, 2000; Kawakami *et al.*, 2001), the primary auditory cortex (Kudoh and Shibuki, 1994, 1997) and the motor cortex (Baranyi and Szente, 1987; Castro-Alamancos *et al.*, 1995; Hess and Donoghue, 1994, 1996) as well as in the prefrontal cortex (Hirsch and Crepel, 1990). As with synaptic plasticity in the hippocampus, activation of NMDA glutamate receptors is essential for the induction of most forms of neocortical LTP and LTD (e.g. Kirkwood *et al.*, 1993; Castro-Alamancos *et al.*, 1995). Furthermore, by analogy with hippocampal plasticity, the induction of either LTP or LTD in layer II/III of the neocortex depends on the level of postsynaptic depolarization (Artola *et al.*, 1990). Either LTP or LTD could be induced by the same stimulation pattern, depending on the level of depolarization during conditioning. Moreover, the same holds for the dependence of synaptic plasticity on the concentration of intracellular free calcium (Tsumoto and Yasuda, 1996): in neurones of the visual cortex, a stimulation pattern suitable to induce LTP was demonstrated to induce LTD when the effective free calcium was reduced by calcium chelators, i.e. substances binding free calcium (Hansel *et al.*, 1997). In these neurones, the intracellular calcium concentration was higher and decayed more slowly with stimulation protocols inducing LTP than with stimulation protocols inducing LTD (Hansel *et al.*, 1997). Quantitative results concerning the calcium concentration for the induction of either LTD or LTP in the neocortex are not available. However, in the hippocampus, fura-2-based quantification of calcium-dependence of the induction of synaptic plasticity revealed a calcium threshold of about 180 nM Ca^{2+} for the induction of LTD and of about 540 nM for the transition from LTD to LTP (Cormier *et al.*, 2001). These results on the voltage- and calcium-dependence of LTD and LTP are congruent with the "BCM" theory (Bienenstock, Cooper and Munro, 1982). This model of synaptic plasticity proposes that active synapses are potentiated when the total postsynaptic response exceeds a critical value, the modification threshold θ_m, and that active synapses are depressed when the activity is less than θ_m (for review see Bear, 1996).

Moreover, during conditioning the timing of evoked EPSPs and the postsynaptic action potential is essential for the induction of either LTP or LTD (Feldman, 2000). LTP is induced when both events coincide or when the EPSP leads the postsynaptic action potential, whereas LTD is induced when the postsynaptic action potential leads the evoked EPSP. The NMDA receptor seems to be ideally suited as a molecular coincidence-detector, since

it is activated by the presynaptic release of glutamate, only if the postsynaptic membrane is sufficiently depolarized by other mechanisms. This associative signal may be provided by strong synaptic activation or alternatively by postsynaptic action potentials backpropagating along the apical dendrite (Paulsen and Sejnowski, 1999). Since the NMDA receptor is part of a non-selective cation channel with an important calcium conductance (for review see Collingridge and Lester, 1989; Kaczmarek *et al.*, 1997), activation of the NMDA receptor results in the activity-related increase of the intracellular calcium concentration necessary for the induction of synaptic plasticity.

Recent studies indicate that the induction of synaptic plasticity is associated with modulation of the number of functional synapses. During the induction of LTP in the visual cortex, previously "silent" synapses can be activated, whereas during the induction of LTD previously functional synapses can be inactivated (Voronin *et al.*, 1996). In hippocampal neurones, "silent synapses" have NMDA receptors but lack AMPA receptors, which can be acquired rapidly after induction of LTP (Isaac *et al.*, 1995). Conversely, induction of LTD results in an increase of the number of AMPA receptors but in an unaltered number of NMDA receptors (Carroll *et al.*, 1999; for review see Scannevin and Huganir, 2000).

Recent studies revealed not only that long-term synaptic plasticity, i.e. LTP and LTD could be induced in neocortical areas, but that also short-term alterations of synaptic strength may occur. PPF of EPSPs as observed in the visual cortex (Volgushev *et al.*, 1997) as well as PPD of EPSPs as observed in the motor cortex (Thomson *et al.*, 1993) are associated with alterations of the release probability of neurotransmitter. However, conditions known to increase the release of neurotransmitter were less effective in the neocortex compared with the hippocampus, while conditions known to decrease the release probability were similarly effective in the neocortex and hippocampus (Castro-Alamancos and Connors, 1997). These results were interpreted in terms of a relatively high probability of release in the neocortex. Furthermore, STP and STD were also reported to occur in the neocortex (Castro-Alamancos *et al.*, 1995).

Thus, it is evident that the neocortex is susceptible to the induction of transient and persistent modification of synaptic strength and that neocortical synaptic plasticity, in spite of some important differences, shares many features with hippocampal synaptic plasticity. However, there is accumulating evidence that—depending on the neocortical area—axonal connections do not respond homogeneously to conditioning stimulation under at least comparable conditions. Comparison of synaptic plasticity between functionally and cytoarchitectonically different neocortical areas has revealed different susceptibility to the induction of synaptic plasticity. Both, the granular somatosensory cortex and the agranular motor cortex were equally capable of generating LTD as well as STD (Castro-Alamancos *et al.*, 1995). In contrast, the capability of the two areas to generate LTP was unequal: in the somatosensory cortex, "theta burst" stimulation reliably induced LTP, whereas it induced STP in the motor cortex. Induction of LTP in the motor cortex required a reduction of the $GABA_A$ receptor-mediated intracortical inhibition, but the resulting LTP still differed from that in the somatosensory cortex, e.g. by its slow onset. Similarly, unequal capabilities to generate LTP were reported for the auditory and visual cortices (Kudoh and Shibuki, 1997). In this study, whole cell recordings revealed that the postsynaptic depolarization elicited by theta burst stimulation was significantly larger in the auditory cortex than that in the visual cortex. These differences were diminished when horizontal connections in supragranular layers were cut.

3.3. Reorganization of Cortical Maps: Associative Synaptic Plasticity and Stabilization of Cortical Neuronal Networks

LTP and LTD have been implicated as the cellular mechanisms involved in the experience-dependent reorganization of neocortical representational maps (e.g. Garraghty and Muja, 1996; Glazewski *et al*., 1996; Kirkwood *et al*., 1996). In this context, two basic properties of LTP and LTD are of importance: (i) input-specificity, i.e. only synapses are modified that were activated during stimulation of a given input ("homosynaptic plasticity"), and (ii) associativity, i.e. a "weak" input can be modified if it is active at the same time as a separate but convergent input is activated by tetanic stimulation (Bliss and Collingridge, 1993). The latter feature may be of particular importance for the interaction of different inputs, e.g. horizontal and vertical intracortical connections. Synaptic plasticity of horizontal connections within cortical layer II/III is discussed as a mechanism possibly involved in reorganization of cortical maps in the motor cortex (Hess and Donoghue, 1994, 1996), the visual cortex (Hirsch and Gilbert, 1993), and the somatosensory cortex (Lee *et al*., 1991). It was demonstrated in a behavioural study that motor skill learning is at least partly due to LTP-like mechanisms in the motor cortex (Rioult-Pedotti *et al*., 1998). HFS applied to intrinsic horizontal connections in layer II/III of different areas of the visual cortex, i.e. the primary visual cortex and the inferotemporal cortex, resulted in the induction of LTP in the inferotemporal cortex, whereas LTD was induced in the primary visual cortex (Murayama *et al*., 1997). This difference in the susceptibility to the induction of LTP is proposed to be due to differences in the distribution of neurochemicals, e.g. protein kinase-C, implicated with the expression of LTP (for review see Elgersma and Silva, 1999).

Hebbian plasticity is indeed a powerful mechanism for the modification of synaptic strength of vertical and horizontal cortical connections. However, Hebbian plasticity tends to destabilize neuronal activity: strong inputs are further strengthened whereas weak inputs are further weakened, resulting in either excessive discharge or inactivity of neurones. Therefore, supplementary mechanisms are necessary to stabilize neuronal responses within neuronal networks modified during sensory experience. The BCM proposal (see above) of an activity-dependent shift of the LTD-LTP transition threshold θ_m, depending on the level of the postsynaptic discharge rate provides such a stabilizing mechanism: during high postsynaptic activity the threshold for LTP is high, making depression easier and further potentiation more difficult; but after a period of low neuronal activity the threshold for LTP should be low, resulting in a higher susceptibility to the induction of LTP. Indeed, it was demonstrated in the visual cortex that LTP induced in light-deprived animals was stronger than in control animals, whereas the magnitude of LFS-induced LTD in light-deprived animals was significantly less compared to control animals (Kirkwood *et al*., 1996). Weakening of LTD was reversible: the magnitude of LTD returned nearly to control levels when light-deprived animals were exposed to light for two days. These results were interpreted in terms of a light deprivation-dependent promotion of LTP over LTD by a shift of the LTD-LTP transition threshold θ_m.

Additional candidate mechanisms important for stabilization of Hebbian plasticity have been proposed: synaptic scaling, spike-timing dependent plasticity (STDP) and synaptic redistribution (for review see Abbott and Nelson, 2000). Synaptic scaling, a mechanism globally modifying synaptic strength, was demonstrated to occur in cultured neocortical networks (Turrigiano *et al*., 1998). In these experiments, blocking spontaneous discharge activity caused a multiplicative increase of synaptic strength in all afferents, whereas

enhancing spontaneous activity caused a multiplicative decrease of synaptic strength. An important component of synaptic scaling is the postsynaptic modification of available functional glutamate receptors. Activity manipulation scales both AMPA and NMDA receptor-mediated transmission (Watt *et al*., 2000). Scaling of the NMDA receptor may influence the influx of calcium and consequently the LTP-LTD induction threshold in a manner comparable to that proposed by the BCM model.

The importance of STDP as a stabilizing mechanism is suggested by the observation that the induction of either LTP or LTD depends on the temporal order of pre- and postsynaptic activity (see above; Feldman, 2000). This mechanism contributes to the stabilization of neuronal discharge (for review see Abbott and Nelson, 2000), since only inputs that discharge in a narrow time window before the postsynaptic discharge are potentiated whereas inputs that fire in a wider time window after the postsynaptic discharge are depressed. When presynaptic action potentials arrive randomly in time with respect to the postsynaptic discharge, LTD dominates over LTP. This was demonstrated in layer II/III pyramidal neurones of the somatosensory (barrel) cortex (Feldman, 2000). In this study, random pairing of pre- and postsynaptic activity resulted in an overall reduction of synaptic strength. STDP leads to a non-uniform distribution of synaptic strengths and to irregular postsynaptic firing on a reasonable average rate. Thus, STDP stabilizes Hebbian plasticity and leads to a noisy but temporally-sensitive state (Abbott and Nelson, 2000).

The occurrence of synaptic redistribution as a stabilizing mechanism is suggested by the observation that postsynaptic LTP acts presynaptically to modify the probability of transmitter release (for review see Abbott and Nelson, 2000). In neocortical pyramidal neurones, an increase of synaptic response was observed only when a synaptic input occurred at low frequency, an effect that was interpreted in terms of a redistribution of the available synaptic efficacy (Markram and Tsodyks, 1996). In the visual cortex, postsynaptic intracellular tetanization resulted in LTP of inputs with strong PPF (low release probability) but in LTD of inputs with small PPF (high release probability) (Volgushev *et al*., 1997). This mechanism, probably involving a retrograde messenger, allows Hebbian modification to act on transient activation without increasing the steady-state response or the steady state excitability of postsynaptic neurones, since it increases the probability of transmission early in a sequence of activity, but decreases the availability of releasable transmitter late in a sequence. Thus, this mechanism additionally influences the short-term dynamics of synaptic transmission. Short-term synaptic dynamics of vertical and horizontal intracortical connection as observed in the barrel cortex may be involved in cortical reorganization by sensory experience (Finnerty, Roberts and Connors, 1999).

Taken together, a variety of mechanisms may contribute to experience-dependent modification of cortical representational maps. Associative long-term synaptic modifications, i.e. LTP and LTD of vertical and horizontal connections are suited to expand or shrink receptive fields of cortical neurones. In this context the activation of "silent synapses" has to be considered of high importance. Stabilization of the discharge level of cortical neurones that is modified by Hebbian synaptic plasticity may be brought about by synaptic scaling, spike timing-dependent synaptic plasticity and synaptic redistribution. The latter and other short-term mechanisms of synaptic plasticity may also be important for the selective sensitivity of cortical neurones to dynamic changes of afferent activity.

Furthermore, mechanisms involved in experience-dependent reorganization of cortical representational maps may include short-term and long-term modification of the synaptic

efficacy of inhibitory input to cortical neurones, since it is generally accepted that inhibitory surrounds and subthreshold contributions determine the receptive field size, i.e. by a dynamically maintained balance between excitatory and inhibitory inputs. However, studies on this subject are scarce: in the visual cortex long-term modification of inhibitory synaptic transmission was demonstrated to occur in the developing visual cortex (Komatsu and Iwakiri, 1993). This form of LTP is not voltage-dependent, but depends on the activation of $GABA_B$ and monoamine receptors (Komatsu, 1996). Short-term alterations of the efficacy of inhibitory synapses have also been demonstrated to occur. PPF and PPD of inhibitory afferents were induced in the somatosensory cortex depending on the pulse interval (Fleidervish and Gutnick, 1995). PPF of IPSPs was induced when pulses were delivered at a brief interval, while PPD was induced when the interval was long. Synaptic depression induced by prolonged stimulation of afferents to cortical neurones was suggested to depend on the depletion of synaptic vesicles (Galarreta and Hestrin, 1998). In these experiments, sustained activation of neuronal afferents resulted in much weaker depression of synaptic currents at inhibitory synapses than at excitatory ones. The differential depression at excitatory and inhibitory synapses in the visual cortex indicates that the balance between excitation and inhibition can change dynamically as a function of activity (Varela *et al.*, 1999). These alterations of the balance between excitation and inhibition may contribute importantly to the reorganization of cortical maps.

4. SUMMARY AND OUTLOOK

We have reviewed recent findings about plastic changes in adult early sensory and motor cortices, that were induced by different approaches including peripheral lesions, differential use, and training. Generally, massive and enduring reorganizations have been described for all areas discussed, confirming the contemporary view according to which all cortical areas are modifiable, beyond the critical sensitive periods during development. The findings demonstrate impressively that the sensorimotor cortical representations in adults are not hard-wired, but retain a self-organizing capacity operational throughout life.

On the other hand, for all forms of plasticity described, there also exist distinct modality-specific differences. These differences include the magnitude of changes, the readiness of inducability, and the specificity of neural parameters that are affected. While plasticity in somatosensory and auditory cortex share many features, many lines of evidence suggest that visual cortex plasticity is characterized by a number of particularities. There exist also a number of area and modality-specific properties of cellular mechanisms mediating plasticity of synaptic transmission, indicating that dissimilarities observed at a systemic level are also present at the cellular level. Assuming that cortical plasticity in adults represents an ubiquitous feature required for survival of an individual, the emerging differences are difficult to understand.

In the following, we offer a number of possible explanations touching on different levels of abstraction of possible underlying mechanisms and functional constraints.

1. From a mechanistic point of view, different forms and magnitudes of plastic changes might be due to differences in cellular, pharmacological and histochemical properties, that reflect specific areal-specific constraints of the molecular equipment present in an area (Huntley *et al.*, 1994; Elgersma and Silva, 1999). While this can explain

existing differences in the outcome of plastic changes, the question remains, what are the reasons for the emergence of such differences in cellular properties?

2. Besides cellular and pharmacological aspects, anatomical particularities can have a decisive impact on the outcome of plastic changes. The network of horizontal long-range connections is a particularly interesting candidate for mediating specific forms of alterations of synaptic efficacy. Differences in the overall pattern of horizontal connections in different areas would explain differences in reorganizations observed both cellularly and at a systemic level.
3. From *in-vitro* experiments evidence has been accumulated that there exist a number of different mechanisms controlling and stabilizing the outcome of plastic processes. Among these, spike-timing effectively controls synaptic potentiation (Abbott and Nelson, 2000). Given the profound area- and modality-specific differences in the timing of the afferent inflow of information (see also Dinse and Schreiner, this volume), it appears conceivable that such mechanisms are highly suited to govern the effectiveness of input-dependent plastic reorganizations.
4. Similarly, the Bienenstock-Cooper-Munro model – BCM (Bienenstock, Cooper and Munro, 1982) provides a mechanism that controls the transition from synaptic depression to synaptic potentiation, by means of the level of the postsynaptic discharge rate. Active synapses are potentiated when the total postsynaptic response exceeds a critical value, the modification threshold θ_m, and synapses are depressed when the activity is less than θ_m. As the level of postsynaptic activity can be regulated in a complex way by selecting and integrating inputs from many different sources, the BCM model can potentially regulate the threshold for inducing diverse forms of plasticity, including the failure to induce any changes.
5. Reorganization in early sensory areas is modified by so-called "top-down" routes conveying information about cognitive and attentional aspects processed in high-level areas, as exemplified by the modulatory action exerted by the cholinergic system. It is possible that differences in the reorganizational outcome are due to a differential sensitivity to this top-down modulation, thereby establishing a differential effectiveness of input- *vs.* attentional-driven plasticity.
6. In somatosensory plasticity, the aspect of "use" and "no-use" provide the key features that allows an easy and intuitive description and classification of plastic changes. Given the obvious lack of typical "use-dependent" plasticity in the visual domain, it is quite possible that the scheme of differential use is an inappropriate concept that does not fit to the specific constraints of the visual system. By the same token, searching for adequate driving forces that are particularly effective in the visual system might allow one to reveal a specific form of visual cortex reorganization.
7. The visual cortex is characterized by a number of so-called functional maps, that are overlaid across the retinotopic gradient, thereby generating a highly complicated form of topological structure (Malach, 1994; Swindale *et al.*, 2000). Up to now comparable topological features have not been described for the somatosensory and auditory cortex (see also Dinse and Schreiner, this volume). It is suggested that these global topological constraints impose forces that stabilize the underlying cortical networks (Wolf and Geisel, 1998), thereby limiting and restricting plastic changes, particularly those of receptive fields. Consequently, only under severe circumstances such as lesions or massive changes of input statistics, do distinct changes of receptive fields or other parameters of neural response properties develop.

8. Neural changes as a consequence of adaptational mechanisms include a large variety of both spatial and temporal parameters of neural response characteristics. However, even under normal conditions, i.e. without involving adaptive processes, sensory processing and how performance is coded is only poorly understood. As a consequence, perceptual learning or training can be accompanied by rather unexpected changes. Conceivably, an apparent lack of plastic capacities might simply reflect hidden changes in parameter regimens presently not recognized or understood. In other words, there can be significant changes, but we do not see them.
9. Finally, it is possible that part of the observed dissimilarities reflect genuine modality-specific differences, building on important constraints associated to the processing of sensory-specific information or constraints emerging from anatomical and morphological requirements, that in turn evolved in response to the processing requirements of a sensory area. Consequently, comparative studies focusing on modality-specific features of cortical plasticity will reveal insights into principles governing neocortical organization.

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