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CHAPTER 7

Cortical plasticity and rehabilitation

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Abstract: The brain is constantly adapting to environmental and endogenous changes (including injury) that occur at every stage of life. The mechanisms that regulate neural plasticity have been refined over millions of years. Motivation and sensory experience directly shape the rewiring that makes learning and neurological recovery possible. Guiding neural reorganization in a manner that facilitates recovery of function is a primary goal of neurological rehabilitation. As the rules that govern neural plasticity become better understood, it will be possible to manipulate the sensory and motor experience of patients to induce specific forms of plasticity. This review summarizes our current knowledge regarding factors that regulate cortical plasticity, illustrates specific forms of reorganization induced by control of each factor, and suggests how to exploit these factors for clinical benefit.

Keywords: Cortical plasticity; Experience-dependent plasticity; Cortical reorganization; Neuromodulators; Cholinergic; Rehabilitation

Factors that regulate plasticity

Plasticity is the remarkable ability of developing, adult, and aging brains to adapt to a changing world. This potential is revealed whenever an organism must meet a new environmental demand or recover from nervous system damage. Plasticity occurs in sensory and motor systems following deprivation of input or overstimulation, increased or decreased usage, learning of new skills, and injury. These experience-dependent changes can be as subtle as a change in neuronal excitability (Engineer et al., 2004) or as dramatic as the rewiring of auditory cortex to process visual information (Sur et al., 1988). Topographic maps, receptive field (RF) size, neuronal firing rate, temporal precision, and combination sensitivity can all be modified by our experiences. The types of plasticity activated by specific situations depend on the nature of the experiences and their behavioral significance, conveyed by release of modulatory neurotransmitters (Fig. 1).

Attentional modulation

Neural plasticity is essential for adapting to changes in the environment but plasticity can be destabilizing if not well regulated. Limiting plasticity prevents meaningless events from driving changes that could degrade previously acquired memories and skills. Attention plays a key role in the regulation of plasticity associated with sensory experience. Repeated sensory stimulation alters topography in primary sensory cortex only when monkeys use the stimuli to make behavioral judgments (Recanzone et al., 1992, 1993). Many studies have shown that cortical neurons respond differently to attended versus unattended stimuli. Neurons in secondary somatosensory cortex, for example, exhibit greater response synchronization when monkeys are engaged in a tactile task (Steinmetz et al., 2000). Attention can also directly affect

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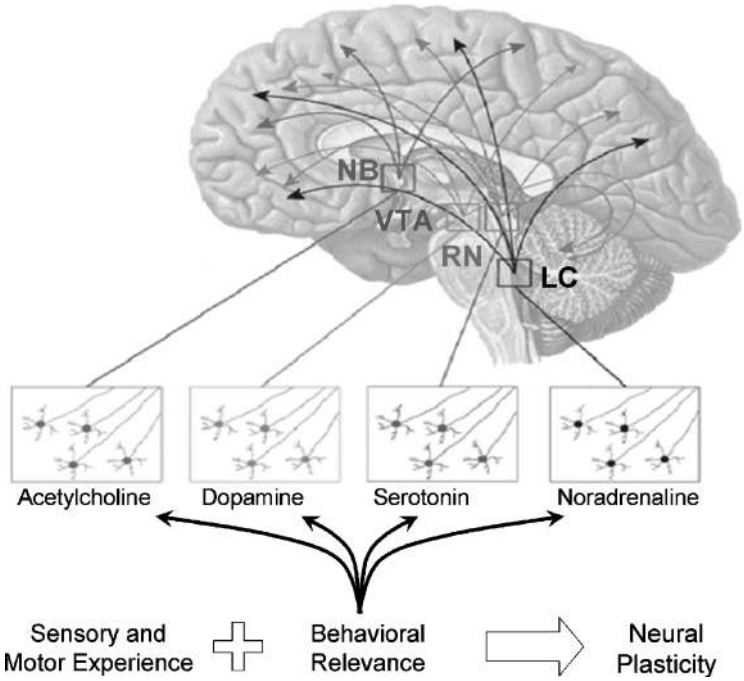

Fig. 1. Several neurotransmitter systems which project widely into the cortex are implicated in learning and experience-dependent plasticity: Acetylcholine from the cholinergic nucleus basalis (NB), dopamine from the ventral tegmentum (VTA), noradrenaline from the locus coeruleus (LC), and serotonin from the raphe nuclei (RN). In addition to these major neurotransmitters, GABA-ergic projections, histamine, and neuro-hormones also play a role in modulating plasticity. Release of these transmitters is normally regulated by behavioral state but can also be triggered by drugs or direct electrical stimulation. Cortical plasticity results when release of these transmitters is repeatedly associated with the occurrence of a sensory stimulus. (*Source*: Figure adapted from McEwen BS, 2003, Karger Gazette, No. 66, Basel, S. Karger AG.)

QA :3

firing rates of cortical neurons (Treue and Maunsell, 1999; Recanzone and Wurtz, 2000). Results from several psychophysical studies support the hypothesis that attention regulates cortical plasticity and learning. Distinct forms of perceptual learning result when subjects attend to different features of an otherwise identical sensory input (Ahissar and Hochstein, 1993). Exposure to moving dot patterns can improve motion direction discrimination ability even if the motion is undetectable (due to low coherence), as long as the subjects are actively engaged in a visual task (Watanabe et al., 2001; Seitz and Watanabe, 2003). These results suggest that directed attention facilitates the learning of associated sensory features.

Neuromodulatory influences

Several neuromodulators, such as dopamine, norepinephrine, and acetylcholine, are known to regulate learning and memory in humans (Hasselmo, 1995). The observation that synaptic plasticity is also enhanced by the presence of these neurotransmitters supports the relationship between learning and plasticity (Singer, 1986; Brocher et al., 1992). Injection of acetylcholine or norepinephrine directly into visual, somatosensory, or auditory cortex during sensory stimulation can promote expression of neural plasticity in the intact brain (Greuel et al., 1988; McKenna et al., 1989; Delacour et al., 1990). Pairing sensory inputs with electrical activation of the nucleus basalis (NB), locus coeruleus (LC), or ventral tegmental area (VTA) also results in plasticity that is specific to features of the associated input (Kilgard and

Merzenich, 1998; Bouret and Sara, 2002; Bao et al., 2003). Stimulation of neuromodulatory neurotransmitter release by amphetamine enhances cortical plasticity in human subjects (Dinse et al., 2003; Tegenthoff et al., 2004). Since release of these neurotransmitters is normally triggered by behaviorally arousing events, it is likely they contribute to the regulation of cortical plasticity.

Patterns of sensory activation

Many studies have shown that sensory input determines the form of cortical reorganization. When animals or humans repeatedly practice a skill that engages a limited region of the sensory epithelium, the regions of the cortical map that respond to task-specific inputs are enlarged (Jenkins et al., 1990; Recanzone et al., 1992, 1993; Elbert et al., 1995; Sterr et al., 1998). Cortical RFs can narrow or broaden and response latency can increase or decrease depending on the spatial and temporal pattern of sensory activation encountered during training. Owl monkeys trained on a tone frequency discrimination task have A1 neurons with smaller RFs and longer response latencies than untrained controls (Recanzone et al., 1993). Monkeys trained to detect changes in the rate of a tactile vibration exhibit larger RFs and faster response latencies (Recanzone et al., 1992). In contrast, training on a task with stimuli that move across the skin cause RFs to shrink (Jenkins et al., 1990). Training on a visual orientation task increased the steepness of orientation tuning in the trained region of the visual field (Schoups et al., 2001). These studies support the hypothesis that perceptual learning and cortical plasticity are specific to attended sensory features.

The rodent whisker system has proven particularly useful for directly comparing how cortical plasticity is shaped by different spatial patterns of activity. If all but one whisker is cut, for example, the responsiveness of the spared whisker is increased (Glazewski et al., 1998). Cutting a single whisker reduces input to the corresponding region of barrel cortex, decreases the responsiveness of the deprived neurons, and increases the responsiveness to neighboring whiskers. If all the whiskers are cut, the reduction in the response to the principle whisker is more modest. A checkerboard deprivation pattern causes responses to the deprived whiskers to decrease, but does not increase the response to the spared whiskers (Wallace and Fox, 1999). Finally, cutting all but two neighboring whiskers causes the RF of neurons in each region to shift toward the other spared whisker (Diamond et al., 1993). These results suggest that competition between sensory inputs induces the different forms of changes in responsiveness.

Timing of sensory inputs

The temporal coincidence of sensory stimulation can be just as important as its spatial pattern in determining the direction and magnitude of cortical plasticity. Inputs that are correlated in time are more likely to cause a change in neural responses than uncorrelated inputs. Simultaneous activation of an area of skin with a vibrating disc increased RF size in primary somatosensory cortex, while stimulation of a single point on the skin does not cause any change (Godde et al., 1996). Simultaneous activation of the developing auditory system by repeated exposure to broadband noise causes increased cortical RFs and degraded tonotopic maps (Chang and Merzenich, 2003). Such changes are not seen after equivalent exposure to tones. Increased simultaneous activation of the fingers due to surgical fusion or operant training leads to large, multidigit RFs in somatosensory cortex (Allard et al., 1991; Wang et al., 1995). This finding suggests that the usual segregation of each digit's cortical representation reflects the normally asynchronous activation of each digit. In vitro and more recently in vivo studies have further demonstrated that the time window for correlated inputs to induce plasticity is on the order of tens of milliseconds (Tsodyks, 2002; Dan and Poo, 2004). These results indicate that the precise spatial and temporal pattern of inputs shape cortical networks due to operation of Hebbian synaptic plasticity.

Duration of experience

Many factors regulate the time course of learning and plasticity (Ebbinghaus, 1885; Dubnau et al., 2003). Fear conditioning can induce rapid and long lasting shifts of neuronal tuning toward the frequency of the conditioned tone (Bjordahl et al., 1998; Weinberger, 2003). In contrast, plasticity following skill learning or use-dependent plasticity develops gradually over time. The magnitude of effects often depends on duration of training and correlates with performance accuracy (Pleger et al., 2003). Motor map reorganization, which is accompanied by synaptogenesis and believed to underlie consolidation of motor skills, occurs during the late phase (after 10 days) of motor skill learning (Kleim et al., 2004). The schedule of inputs can also determine the induction of stable versus reversible synaptic modifications (Mauelshagen et al., 1998). Spaced repetition of LTP inducing stimuli prevents the reversal of LTP due to subsequent spontaneous activity that occurs after massed repetition (Zhou et al., 2003). Stable synaptic modifications are also induced by visual experience when the exposure to unidirectional moving bars occurs in a spaced pattern (three sets of 60 flashes separated by 5 min) versus massed pattern (180 flashes continuously). If persistent synaptic changes are important for learning and memory, the effective use of training strategies that prevent their reversal is important. In behaviorally trained mice temporally spaced training more effectively recruits protein synthesis and enhanced long-term memory of contextual conditioning, while massed training triggers greater protein phosphatase 1 activity which suppresses memory formation (Genoux et al., 2002; Scharf et al., 2002). These results suggest that the schedule of training determines the duration of neural plasticity and learning.

Influence of background stimuli on plasticity

Psychologists and psychophysicists have known for decades that unattended background stimuli (context) influence perceptual learning. Studies of sensory plasticity have typically been conducted in environments stripped of context, by using soundproof booths or gray backgrounds. Recent experiments in more naturalistic and complex settings have shown that context also influences plasticity.

In many cases, adding complex backgrounds actually improves learning. Contrast discrimination learning, for example, can be facilitated by fixed contrast stimuli flanking the target stimulus (Adini et al., 2002). Dim line objects are easier to detect when flanked with a second collinear bar (Kapadia et al., 1995). This improvement in human performance is paralleled an enhancement of neuronal responses in monkey V1 when equivalent visual stimuli are presented (Kapadia et al., 1995). When foot shock is paired with a tone, the presence of unpaired background tones determines whether auditory cortex neurons shift their frequency tuning toward or away from the paired tone (Bakin and Weinberger, 1990; Ohl and Scheich, 1996; Dimyan and Weinberger, 1999).

While all of these studies suggest that many factors regulate plasticity and learning, direct comparison of the interactions between these factors has proven difficult. Differences in the behavioral response, task difficulty, task goal, motivation, modality and species often confound the influence of the discussed factors on plasticity. Because these factors are so tightly interdependent it has been difficult to tease apart their relative importance in directing different forms of plasticity. Varying sensory patterns or adding a complex background, for example, would also affect task difficulty in most cases. Currently, reduced preparations provide the best opportunities to study the interactions between each of the factors that regulate neural plasticity. Experimental paradigms that directly stimulate modulatory systems have proven particularly valuable in documenting the influence of stimulus pattern, timing, and background conditions on cortical plasticity.

Sensory input paired with controlled release of neuromodulators

Pairing electrical activation of the cholinergic NB with different sounds generates changes in cortical map and RF properties in rats that closely parallel

the different forms of plasticity resulting from operant training in monkeys. For example, temporally modulated stimuli tend to *increase* RF size, while stimuli that activate different regions of the receptor surface tend to *decrease* RF size (Kilgard et al., 2002). While the differential plasticity observed in operant studies could be attributed to any number of technical differences, in the NB stimulation experiments the only explanation for the differential plasticity was the temporal and spectral properties of the sounds associated with NB stimulation. The observation that similar sensory inputs lead to comparable plasticity even in the absence of operant training supports the conclusion that sensory features determine the form of cortical plasticity.

During natural learning, changing task contingencies are known to alter the type, amount, and timing of neuromodulator release. For example, novel sounds activate cholinergic NB neurons for a few trials, but habituate rapidly (Richardson and DeLong, 1990, 1991). The response can later be reinstated if the sound is associated with a reward or punishment. NB releases acetylcholine onto the cortex only during the learning phase of a lever press task, but not after the task is well learned (Orsetti et al., 1996). Electrical stimulation bypasses the natural triggers of NB activity and eliminates the natural brake on cortical plasticity. The consistency of electrical activation makes it possible to systematically compare how the type, amount, and timing of neuromodulator release influence cortical plasticity when associated with sensory stimuli of differing spatial and temporal properties.

Patterns of activation determine type of reorganization

Distinct types of cortical reorganization are generated when NB stimulation is associated with different sensory inputs. Cortical topography, RF size, and response timing are altered as a function of the temporal modulation and spatial distribution of inputs associated with NB stimulation. The focal activation caused by presentations of a single tone frequency results in expansion of the area responsive to the tone, and modest RFs broadening. Distributing the activation over more frequency sectors (i.e., seven tone frequencies) prevents the map reorganization but results in a narrowing of RFs (Kilgard et al., 2001). Rapidly modulated tone trains cause map expansion and dramatic RF broadening when activation is focal (i.e., one carrier frequency) and less extreme RF broadening and no map plasticity when the tone trains activate several regions (i.e., seven different carrier frequencies). These results document how different activation patterns direct cortical plasticity: (1) sensory map expansion only results when sensory activation is focal. (2) Distributing inputs across the cochlea tends to reduce RF size. (3) Modulated stimuli tend to increase RF size compared to unmodulated stimuli (Table 1, Kilgard et al., 2002). The observation that RF size is increased by stimuli with high degree of temporal modulation and little spatial variability (tone trains) and decreased by stimuli with high spatial variability and no temporal modulation (unmodulated tones of varying frequency) is consistent with earlier observations of plasticity in operant trained monkeys (Recanzone et al., 1992, 1993). These results indicate that NB stimulation directs changes that are

Table 1. Plasticity induced by pairing NB with different sounds

NB stimulation paired with	Plasticity observed	References
Single tone	Map expansion + decrease latency	Kilgard and Merzenich (1998)
Tone train	Map expansion + decrease latency + RF broadening	Kilgard and Merzenich, 2001 QA:5
Distributed tones	RF narrowing + increase latency	Kilgard and Merzenich (1998)
Distributed tone trains	RF broadening + temporal plasticity	Kilgard and Merzenich (2001)
Frequency modulated tones	RF broadening + decrease latency + decreased thresholds	Moucha et al. (2005)
Complex acoustic sequence	Combination sensitivity + decrease latency + decreased thresholds	Kilgard and Merzenich (2002)
Background sounds	Alters plasticity generated in silence	Moucha et al. (2005)

similar to operant induced plasticity even though the rats did not use the stimuli in any way.

Natural sounds usually vary both in spatial and temporal structure and create more complex activity patterns than tones. Pairing frequency modulated sweeps and complex acoustic sequences leads to forms of plasticity that are unpredictable from earlier studies with simple tones (Kilgard and Merzenich, 2002; Moucha et al., 2005). FM sweeps result in a moving pattern of activation across the cochlea. Although tones and FM sweeps may share many features in common (including starting frequency, bandwidth, intensity, duration), pairing FM sweeps with NB stimulation causes different plasticity compared with unmodulated tones. Pairing FM sweeps with NB decreases response latency, broadens RFs, and increased sensitivity to quiet tones. These changes are restricted to the region of A1 activated by the sweep, but no map expansion results. When the starting frequency of the FM sweeps is varied no plasticity is observed in any region of A1 (Moucha et al., 2005). While repeated exposure to FM's does not cause any preference for FM direction (increasing or decreasing), pairing a sequence of sounds with identical NB stimulation can result in the development of responses sensitive to tone order.

Although plasticity mechanisms have presumably evolved to increase cortical processing capacity for behaviorally relevant inputs, it is not immediately obvious why the plasticity associated with each spatial and temporal input pattern is beneficial.

Correlation of sensory inputs

Studies in auditory, visual, and somatosensory cortex have suggested that input correlations strongly influence neural plasticity (Buonomano and Merzenich, 1998). In the developing visual system, for example, alternating asynchronous electrical stimulation of the optic nerve prevents normal development of binocular visual responses (Stryker and Strickland, 1984). In auditory cortex, sounds designed to decrease or increase correlation across the frequency map lead to very different forms of plasticity (Pandya et al., 2005). Alternating activation of two nonoverlapping auditory neuron populations by two tones of distant frequencies (2 and 14 kHz) results in map segregation, decreased excitability, and longer response latencies of the activated neurons. These changes do not occur when NB-stimulation is paired with a modulated noise burst that synchronously activate large populations of A1 neurons. Pairing pulsed noises with NB stimulation disrupts tonotopic maps and reduces spontaneous discharge correlation in the primary auditory cortex (Bao et al., 2003). These finding are in agreement with the Hebbian postulate that inputs with decreased correlation weaken cortical responses and supports other observations that primary sensory cortices segregate inputs that are asynchronous and integrate correlated inputs (Allard et al., 1991; Wang et al., 1995).

Duration of associative sensory pairing

The duration of NB-induced plasticity depends on the schedule of the pairing protocol. Repetitively pairing NB stimulation with a tone for several minutes causes a shift in frequency tuning that reverses within 5 h (Zhang et al., 2005). Cortical map expansion builds with repeated pairings. One month of 300 NB-tone pairings per day increases the A1 representation of the paired frequency by twice as much as a week of pairing (Kilgard and Merzenich, 1998). After a month of pairing, NB-induced map plasticity endures for at least 20 days (Carrasco et al., 2004). NB stimulation also increases the duration of cortical and subcortical plasticity induced by cortical microstimulation (Ma and Suga, 2003). These results support earlier observations that cholinergic modulation contributes to both short-term and long-term plasticity.

Background stimuli influence plasticity outcomes

Although background stimuli are known to influence task performance and plasticity (Kapadia et al., 1995; Adini et al., 2002), it has not been clear whether the differences are due to altered task difficulty or to some specific influence of the dis-

tracters. By directly pairing sensory stimuli with NB stimulation in different contexts, we have shown that background stimuli can influence plasticity independent of any influence on task performance.

Background sounds can alter bandwidth, threshold, and map plasticity. The 20% increase in RF size that occurs after pairing a single tone with NB stimulation does not occur if the same tone-NB pairing is interleaved with flanking tones that are not associated with NB stimulation (Kilgard et al., 2001). Repeated presentation of the word /SASH/ paired with NB stimulation causes expansion of the high frequency region of A1 (Pandya et al., 2003), presumably because the first element of the word is the high frequency /S/ sound. This map plasticity is eliminated when each phoneme of the word /S/, /A/, and /SH/ are also presented, but not paired with NB stimulation. Finally, the addition of unpaired FM sweeps that contrast the duration and direction of the paired FM sweeps results in threshold and latency plasticity not observed if the identical FM's sweeps are paired with NB stimulation in a silent background (Moucha et al., 2005). These results indicate that background conditions, previously thought to be irrelevant, are likely to shape many forms of cortical plasticity.

Clinical conclusions

It was proposed two decades ago that cortical reorganization after injury may be the neural substrate for recovery of function after brain damage (Jenkins and Merzenich, 1987). More recent studies in primates have shown that rehabilitative training can direct reorganization to benefit recovery (Nudo et al., 1996). There is no longer a doubt that reorganization after brain lesions is shaped by the sensorimotor experiences in the weeks to months following injury. Hence it is important to effectively manage plasticity after brain damage. Many of the factors that influence plasticity can be manipulated in clinical settings to enhance therapeutic outcomes.

Attention is often impaired after brain injury and likely plays a critical role in directing training-induced plasticity. Patients with the highest vigilance scores typically receive greatest benefit from the rehabilitation therapy (Sohlberg et al., 2000). Some strategies, such as constraint therapy, that increase arousal (and even frustration) can be more effective than traditional occupational therapies (Taub and Uswatte, 2003).

The diffuse modulatory systems including the cholinergic NB are particularly vulnerable to dysregulation after brain damage. Experimental damage to the NB prevents map reorganization and retards skill learning in rats (Fig. 2). The recent observation that NB damage also prevents recovery from brain damage suggests many of the same mechanisms that regulate normal learning also regulate recovery from injury (Conner et al., 2005). In some patients, medication may be beneficial for normalizing attentional and neuromodulatory mechanisms. Agents that stimulate neuromodulators known to place the brain in a permissive state for experience-dependent changes are most likely to be effective.

Drugs that act on noradrenergic, dopaminergic, serotonergic, and cholinergic systems have been shown in laboratory and clinical research to be pharmacological adjuvants in neurorehabilitation (Phillips et al., 2003). Amphetamines lead to a diffuse increase of several modulators and can have a positive influence even when administered only as a single dose at the beginning of therapy (Feeney et al., 1982). It is important to note that drug administration only aids recovery when paired with practice. Amphetamine administration during speech language therapy increases the rate of improvement of aphasic patients during the early recovery period after stroke (Walker-Batson et al., 2004). Amphetamine also facilitates speech training in adult cochlear implant users (Tobey et al., 2005) and second language acquisition in normal subjects (Breitenstein et al., 2004). More research is needed to evaluate how best to facilitate neurological recovery using nervous system stimulants and other psychoactive compounds.

Since sensory and motor experiences (associated with release of modulatory neurotransmitters) determine the form of plasticity generated, it is critical to develop targeted rehabilitation techniques designed to stimulate adaptive plasticity following

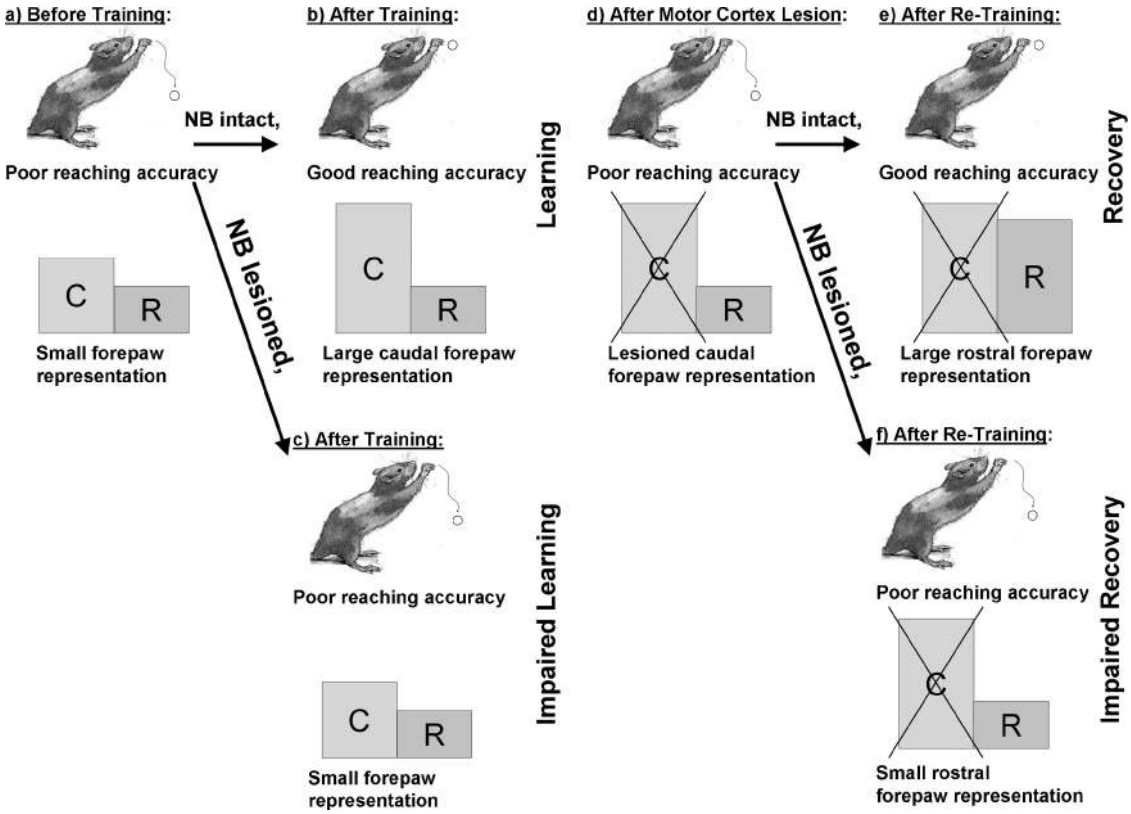

Fig. 2. Rats can improve their grasping skill with repeated practice. After practice more neurons in caudal motor cortex control the trained forepaw (b). Without the normal input from the cholinergic nucleus basalis (i.e., after lesion of NB cholinergic neurons) rats cannot improve their accuracy with training and the motor map of the trained forepaw remains unchanged (c). This result indicates that practice alone without appropriate levels of neuromodulators does not result in learning or map plasticity. Cortical lesions of the caudal forepaw representation after training (d) results in loss of accuracy that can be recovered after retraining and expansion of the rostral motor map of the trained forepaw (e). If nucleus basalis is lesioned during retraining, recovery of reaching accuracy is impaired and the rostral forepaw representation does not change (f). This result indicates that appropriate levels of neuromodulators are also required to promote compensatory plasticity and recovery of function after brain damage. (*Source*: Results illustrated are from experiments by Conner et al., 2005).

QA :4

brain damage. Motor maps are altered by skill acquisition not by repetitive use alone (Nudo, 1997). In somatosensory cortex postlesion changes are related to individual strategies and sensorimotor experience resulting from idiosyncratic behavior. The type of reorganization often depends on the strategy used by individual monkeys to reacquire an object retrieval skill after an experimentally-induced stroke (Xerri et al., 1998). These findings imply that cortical map plasticity can be influenced by the pattern of sensorimotor stimulation during behavioral treatment. In dysphagic stroke patients electrical stimulation of the pharynx results in motor cortex plasticity that is dependent on the pattern of stimulation (frequency, intensity, and duration of stimulation) and correlates with improvement in swallowing function (Fraser et al., 2002). Several treatment strategies now effectively combine modulation of somatosensory input, administration of pharmacological adjuvants, and cortical stimulation to improve outcomes of rehabilitation (Hummel and Cohen, 2005).

The influence of background has not been well-studied in the context of neurorehabilitation. However, studies have documented beneficial

Table 2. Factors regulating plasticity

Factors regulating plasticity	Effect	References
Attention	Enhances stimulus driven plasticity via internal trigger of neuromodulator release	Hasselmo (1995)
Drugs	Achieve optimal levels of neuromodulators required for plasticity	Phillips et al. (2003)
Pattern of stimuli	Determines form of plasticity (reorganization of sensory representations, temporal precision, spatial selectivity, etc.)	Buonomano and Merzenich (1998)
Temporal delivery (spaced vs. massed training)	Potentiation and stabilization of changes by stimulating protein synthesis mechanisms, and reducing phosphatases that prevent long-term changes	Genoux et al. (2002); Scharf et al. (2002); Zhou et al. (2003)
Duration of training	Consolidation of changes via synaptogenesis	Kleim et al. (2004)

effects of general environmental enrichment in recovery after experimental brain infarcts (review Johansson, 2004). Enriched environments further enhance recovery when combined with training or drug therapy (Biernaskie and Corbett, 2001; Puurunen et al., 2001). Our results from plasticity experiments indicate that adding complex backgrounds during rehabilitative training may aid in emphasizing and facilitating performance on specific tasks.

In conclusion, therapies that optimize neural plasticity by integrating all the concepts described above are likely to improve patient outcomes (Table 2). Optimal modulator release can be accomplished by modulating attention and arousal either through task requirements or stimulating drugs. Stimuli used in training can be selected to address specific changes (rewiring) needed to direct recovery of function in individual patients. The proper timing of training sessions (i.e., spaced rather than massed training) and duration should also be optimized for training to be effective and long lasting. The addition of background stimuli may prove beneficial in many situations. This context can be used to emphasize aspects of a task or to incrementally increase task difficulty to maintain the patient's motivation and arousal. Ideally, the progress and efficacy of therapy should be monitored (and adjusted) in each patient using brain imaging or evoked potentials.

We are now beginning to understand how many factors interplay in directing different forms of plasticity. Manipulation of the many parameters known to shape brain plasticity, including the pattern, timing, and duration of events associated with attention and release of modulatory neurotransmitters, is essential to improving neurorehabilitation.

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