The Human brain is only 100,000 years old. Yet, this newly evolved organ endows us with unique creative capabilities beyond all other living creatures, including the gift to understand itself. As our very survival and success in life depends on utilizing our brain's power, intense efforts have begun worldwide to understand the brain, reverse-engineer it and even augment its capacity. Towards this end we harness every trick in the book of mathematics, physics, chemistry, pharmacology, biology, psychology, as well as computer science, information sciences, and engineering – giving rise to the birth to the new *AugCog Era*.

The new AugCog research field focuses on the development of scientifically-based rigorous approaches, including brain-computer interfaces and the use of various drugs, for restoring and augmenting cognition. The field includes the study of the relationship between basic operational states of the brain, such as sleep, or daily activities such as dance and their impact on augmenting cognitive capabilities.

This book confronts our entry into the *AugCog Era* through a series of contributions from the world's best know experts. The book is divided into two sections, the first of which discusses state-of-the-art methodologies; and the last provide some perspective on the social and ethical issues. These two parts are separated by an interlude in cognition, where a fascinating story of the savant syndrome is told.

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Henry Markram is the Project Director of the Blue Brain Project, Director of the Center for Neuroscience & Technology and co-Director of EPFL's Brain Mind Institute (BMI). At the BMI, in the Laboratory for Neural Microcircuitry, Markram has continued his work to unravel the blueprint of the neocortical column, building state-of-the-art tools to carry out multi-neuron patch clamp recordings combined with laser and electrical stimulation as well as multi-site electrical recording, chemical imaging and gene expression. The ultimate aim of his ambitious Blue Brain Project is to simulate the brains of mammals with a high level of biological accuracy and study the steps involved in the emergence of biological intelligence.

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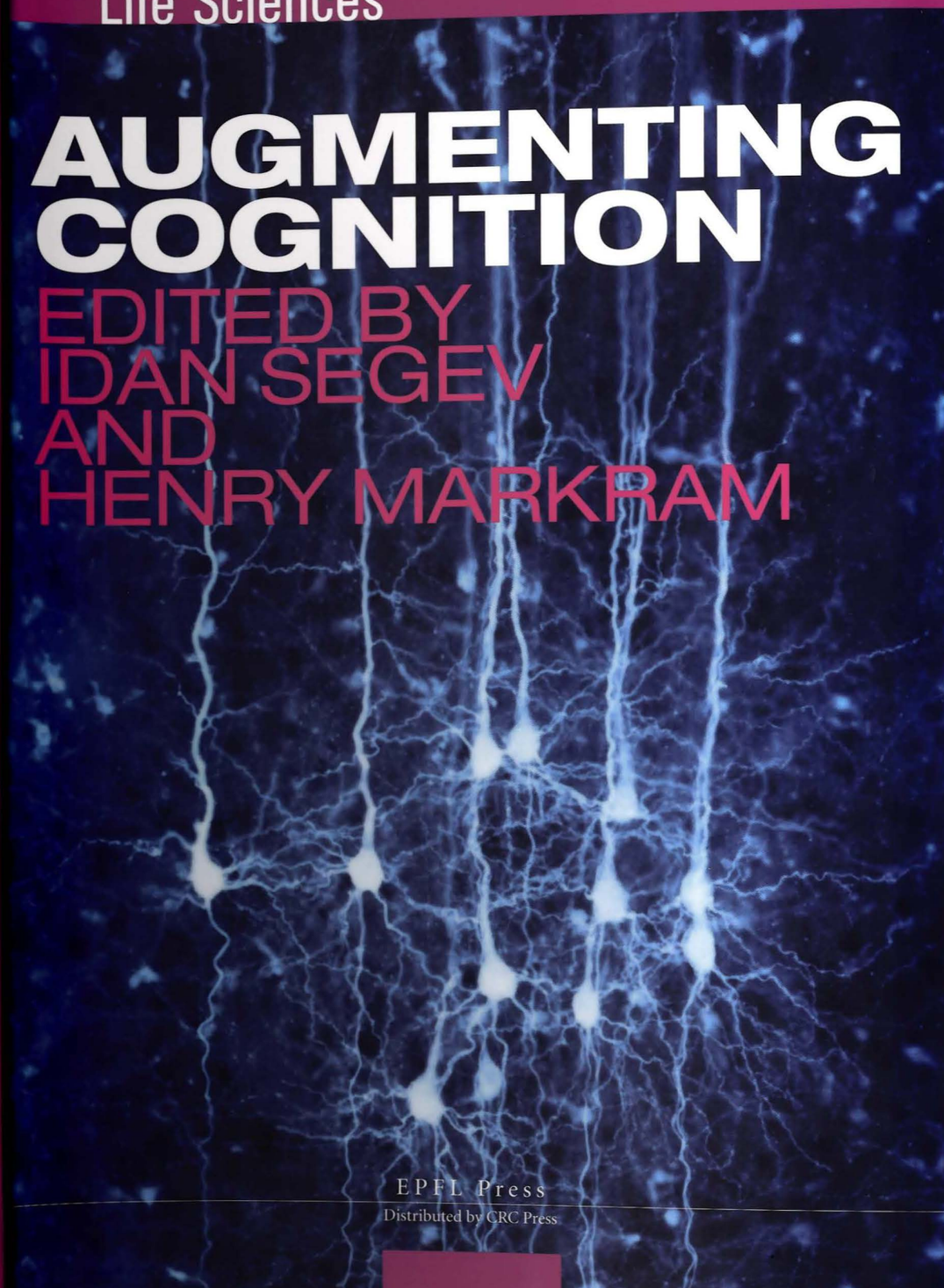

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Life Sciences

AUGMENTING COGNITION

EDITED BY IDAN SEGEV AND HENRY MARKRAM

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1 Sensory Stimulation for Augmenting Perception, Sensorimotor Behavior and Cognition

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1.1 Introduction

Heritable features evolving during evolutional 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, allowing rapid and effective adaptations that are not specified by genetic constraints, are required.

Given these obvious needs for plastic adaptations, it appears only natural that brain plasticity of various forms corresponds to a general and ubiquitous feature present in all sensory and motor modalities. In this context, it is surprising that the notion of adult neuroplasticity has not established itself sooner than the late eighties of the last century. Before that, the neuroscience community conceived adult brains as being non-plastic.

Numerous studies over the last decades have shown that perception, behavior and cognition are not constant, but subjected to manifold modifications throughout a lifespan. Major determinants include development and aging as well as alterations following injury-related brain reorganization. Other sources modifying behavior originate from constraints arising under conditions of everyday-life, e.g., particularities of occupation including life-style and prolonged episodes of heavy schedules of sensory stimulation as exemplarily present in blind Braille readers or musicians. It should be emphasized that, in spite of the substantial amount of plastic capacities, systems must possess a sufficient generic stability to warrant secure processing. Conceivably, there is a trade-off between modifiability and stability.

The gold standard to achieve high-level skills is to undergo long periods of training. For example, it takes several tens of thousands of hours of intense practice to develop musical skills typically observed in professional musicians. Similar numbers also hold for other expert performances in for instance sports. The recent development of non-invasive imaging techniques has made it possible to analyze the impact of training and practice also in humans. These investigations have provided overwhelming evidence that extensive use and practice result in substantial changes of associated cortical representations thus confirming previous data from animal studies. As a result, a large community in neuroscience now deals with brain changes evoked by training and practice to determine properties and mechanisms of neuroplasticity.

Findings from such studies imply that almost every possible action/occupation/training affects brain organization. As a consequence, brains must be regarded as dynamically maintained throughout life. In a way, this makes brains similar to muscles: much usage causes them to expand, while poor use makes them shrink. The new message is that this not only holds for the developmental period, or for functional changes in adults, but also for structural changes during adulthood. So, anything one does leaves a trace in the brain. The dark side of that is that also everything one does not do leaves traces, which implies that the acquisition of skills and capabilities can hardly be maintained without practice. There is no freezing of skills, because the brain machinery underlying them will deteriorate if not active, which has a number of severe implications particularly crucial in the field of aging.

For several years, a new and fascinating discipline has evolved, where neuroscientists now successfully make use of neuroplasticity principles to induce what can be called targeted brain plasticity. This is done by means of protocols that do not rely on the conventional modification of use, training and practice. Instead, by targeting defined brain areas, either through sensory stimulation, or through direct stimulation of the brain (by means of transcranial magnetic stimulation), learning processes can be induced. While, at first glance, such approaches should not work at all, there is now evidence of an almost amazing efficacy, including improvements of simple motor and perceptual tasks, but also much more cognitively demanding abilities.

This chapter will provide a review of recent work where human behavior and perception has been modified through mere exposure, i.e., sensory stimulation protocols incorporating canonical protocols used to alter synaptic transmission and efficacy. In addition, we will briefly summarize alternative attempts based on sensory stimulation with the goal to improve human functions.

1.2 Electric cochlear stimulation

Cochlear prostheses have been used for many years to restore sound perception in patients with profound sensorineural deafness. By electrically stimulating acoustic nerve fibers, the central auditory system can be systematically activated to maintain the capacity for hearing. A first account of this approach can be traced back nearly half a century. When 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. Electrical implant stimulation does not rely on a perfect imitation of normal patterns of peripheral neural activity, but on a re-learning of input patterns arising from an artificial sensory input via electrical stimulation. In this sense, the ability for gaining/re-gaining speech understanding mediated by cochlear stimulation is accomplished by new strategies of cortical processing that serve higher processing stages to interpret new patterns arriving from the periphery. These strategies are thought to emerge from plastic capacities in response to the constraints imposed by the properties of the new input statistics that in turn result from the stimulation strategy employed.

1.3 Vagal nerve stimulation

Animal studies have shown that a pairing of sensory stimuli with electrical stimulation of the cholinergic nucleus basalis generates long-lasting changes in the cortical organization [1]. However, as this

[1] Kilgard MP, Merzenich MM. "Cortical map reorganization enabled by nucleus basalis activity" *Science* 1998;279:1714–1718.

form of intervention is highly invasive, it is not practical for clinical use. As vagal nerve stimulation triggers the release of neuromodulators known to promote plastic changes, it is a less invasive method for generating targeted neural plasticity by pairing vagus nerve stimulation with sensory inputs. Thereby, the efficacy of vagal nerve stimulation in enhancing plasticity seems to lie in the synergistic action of multiple neuromodulators acting in the cerebral cortex and other brain regions. In fact, it was recently demonstrated that in an animal model of tinnitus, where the auditory cortex was degraded by repeated exposure to intense noise, a repeated pairing of tones with brief pulses of vagus nerve stimulation completely eliminated the physiological and behavioral correlates of tinnitus in noise-exposed rats. This suggests that the approach might have potential clinical values [2].

1.4 Virtual reality and augmented reality devices

Virtual reality applications offer new opportunities to study not only brain activation under unusual stimulation conditions, but also for an enhancement of sensorimotor and cognitive functions in humans. Mobility impairment is a frequently encountered phenomenon often observed during aging or in association with neurological diseases such as Parkinson's disease (PD) or multiple sclerosis (MS). Alternative to conventional rehabilitation by physiotherapy or medication, new attempts using closed-loop visual and auditory feedback provided through augmented reality or virtual reality devices have been shown to provide promising routes in the treatment of gait disorders [3].

Subjects have to wear a set of devices consisting of a small measurement-computation unit attached to the patient's clothing, a head-mounted microdisplay, and earphones. The measurement-computation unit is composed of a multiaxial accelerometer, a compass, and a microcontroller. The apparatus, operating in an adaptive closed-loop mode, displays a life-size virtual checkerboard-tiled floor superimposed on the real world by see-through glasses. The closed-loop or feedback concept implies that the speed of the cues is not externally set but is an outcome of the walking speed of the user. The visual effect is the same as that created when walking over earth-stationary cues such as a real tiled floor. Similarly, the rhythm of the auditory cue is determined by the rhythm of the steps, not vice versa.

The next stage involves the user regulating the gait pattern to create a constant optical flow and a rhythmic auditory cue. The virtual,

[2] Engineer ND, Riley JR, Seale JD, Vrana WA, Shetake JA, Sudanagunta SP, Borland MS, Kilgard MP. "Reversing pathological neural activity using targeted plasticity" *Nature* 2011;470(7332):101–104.
[3] Espay AJ, Baram Y, Dwivedi AK, Shukla R, Gartner M, Gaines L, Duker AP, Revilla FJ. "At-home training with closed-loop augmented-reality cueing device for improving gait in patients with Parkinson disease" *J Rehabil. Res. Dev.* 2010;47(6):573–581.

augmented floor responds dynamically to the participant's own motion and "moves" toward him at the speed set by the user as measured by the accelerometer. The tiled floor acts as a moving visual display whose speed is generated in a natural feedback fashion by its own motion. The grid allows the user to step on the tiles with long strides as they walk, though they do not become enlarged or modified based on previous step lengths. A steady gait synchronizes the patient's own steps with the virtual tiles and the auditory cues, thus "rewarding" the user for making the effort. Additional auditory feedback from the patient's own steps is provided through earphones. The auditory feedback is continuous so long as patients are walking steadily, producing a rhythm they hear based on their gait pattern.

This system has been successfully tested in PD and MS patients as well as in elderly individuals characterized by severe gate-related gait impairments. Generally, most albeit not all users demonstrated improvements in walking velocity and stride length, which were maintained after device removal [3]. Nevertheless, more studies are needed to understand the factors contributing to the overall compliance of the system. Independent of this, the use of closed-loop sensory feedback appears to be a new and effective intervention to improve gait and mobility without relying on medication.

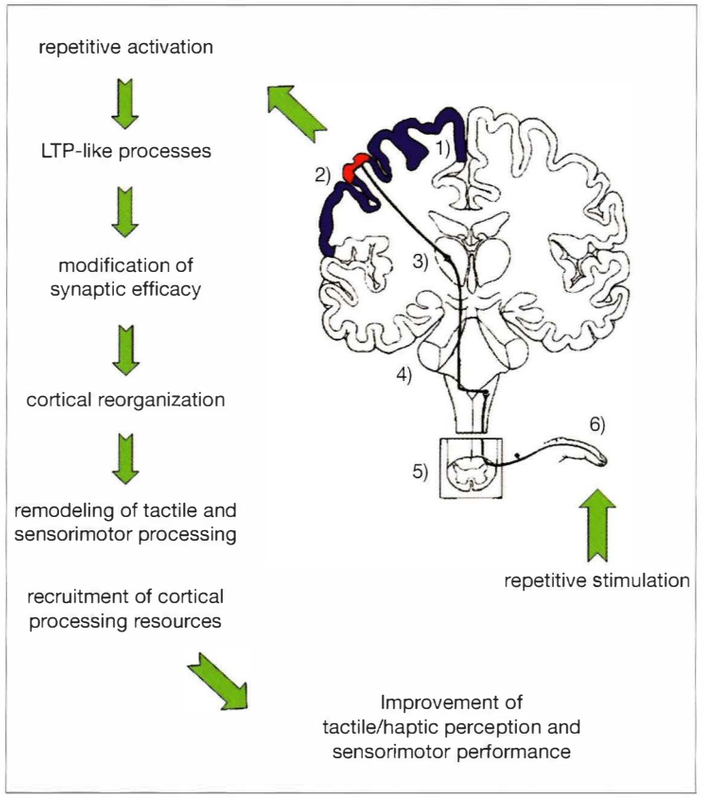
1.5 Rationales for learning through mere exposure

Persistent changes of synaptic transmission constitute the foundations of plasticity and learning. We have therefore developed learning protocols that employ passive stimulation protocols as a measure to induce plastic processes in human subjects. The basic idea is to utilize the broad knowledge we now have regarding brain plasticity to design specific stimulation protocols through which it becomes feasible to purposefully change brain organization and thus perception and behavior. The term "passive" is meant to indicate that a subject is exposed to repetitive sensory stimulation without actively paying attention.

For example, we introduced a so-called "co-activation" stimulation protocol that within hours to minutes induced learning processes in the brain in parallel to a behavioral improvement [4-5]. Co-activation closely follows the idea of Hebbian learning: synchronous neural activity, which is regarded instrumental for driving plastic changes, is generated by the simultaneous tactile "co-stimulation". More recently, we developed alternative protocols focusing on frequency rather than spatial cooperative processes by using high-frequency [6] or

[4] Pleger B, et al. "Functional imaging of perceptual learning in human primary and secondary somatosensory cortex" *Neuron* 2003;40:643–653.
[5] Dinse HR, et al. "Pharmacological modulation of perceptual learning and associated cortical reorganization" *Science* 2003b;301:91–94.
[6] Ragert P, et al. "Differential effects in human tactile discrimination behavior evoked by tactile high- and low-frequency stimulation" *BMC Neuroscience* 2008;9:9.

Figure 1.1
Schematic illustration of the assumed chain of changes evoked by repetitive stimulation. We suggest a cascade of functional alterations within the sensory system being targeted, here representative for the somatosensory system leading to the induction of plastic processes which in turn result in behavioral/perceptual changes. (1) Somatosensory cortex (SI), (2) finger representation in SI, (3) thalamus, (4) brain stem, (5) spinal cord, (6) mechanoreceptors in the fingers.



paired-interval stimulation (Sect. 1.8). In all cases, after passive stimulation for only brief episodes, the perceptual and sensorimotor performance was improved by manipulating the statistics of the input, which presumably induced long-term potentiation, i.e., "LTP-like", and long-term depression, i.e., "LTD-like", processes in the brain (Fig. 1.1).

The last few years, sensory stimulation protocols have gained substantial interest, and are currently investigated as a means of driving learning and plasticity processes. For this reason, several laboratories use a large range of terms such as "peripheral nerve stimulation" [7], "somatosensory stimulation" [8], or "exposure-based learning" [9].

[7] Hummel FC, Cohen LG. "Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke?" *The Lancet Neurology* 2006;5:708–712.
[8] Wu CW, et al. "Influence of electric somatosensory stimulation on paretic-hand function in chronic stroke" *Archives of Physical Medicine and Rehabilitation* 2006;87:351–357.
[9] Beste C, et al. "Improvement and impairment of visually-guided behavior through passive LTP- and LTD-like visual stimulation" *Current Biology* 2011, DOI 10.1016/j.cub.2011.03.065.

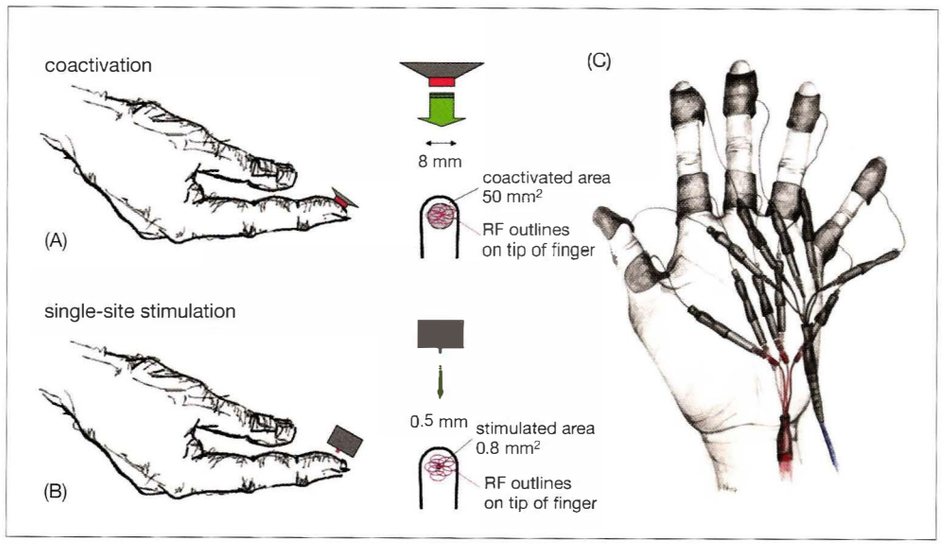
Figure 1.2
(A) Application of coactivation: (top) A small mechanical actuator with a diameter of 8 mm was mounted on the tip of the right index finger to coactivate the receptive fields representing the skin portion under the solenoid (50 mm²). (bottom) Control protocol. Application of a so-called single-site stimulation: A small device consisting of only one tiny actuator (tip diameter 0.5 mm) was mounted on the tip of the right IF to stimulate a single "point" (0.8 mm²). Reprinted with permission from: Dinse HR, et al., *Transactions on Applied Perception* 2005;2:71–88.
(B) Electrical repetitive stimulation of a single finger. Adhesive surface electrodes fixed to the first and third finger-segment transmit electrical pulses (cathode proximal).

We here provide a summary of our studies aimed at improving human tactile perception and sensorimotor behavior through pure exposure to patterned sensory stimulation. As we recently succeeded in demonstrating also a dramatic effectiveness of repetitive stimulation to alter visual guided behavior, we include a brief description of visual repetitive stimulation leading to a sustained improvement of visual perception and behavior.

As a rule, we employ the term "co-activation" for experiments using the initial Hebbian stimulation approach, but the term "repetitive sensory stimulation" for protocols independent of spatial cooperativity that rather utilize frequency and temporal patterning of stimulation. The term "passive stimulation" is used as a more general term and covers approaches similar to "exposure-based learning".

1.6 How it is done – tactile domain: cutaneous and electrical stimulation

Depending on the protocol used, it is possible to stimulate a single finger, or all fingers of a hand. For application of tactile co-activation or tactile repetitive stimulation, a small mechanical actuator is taped to the tip of a finger. The device allows a cutaneous stimulation of the skin portions underneath, thereby co-activating the receptive fields within an area of approximately 1 cm² (Fig. 1.2). In its initial version [4,5], co-activation was applied for 3 hours using stimuli drawn from a Poisson process at interstimulus intervals between 100 to 3000 ms with an average stimulation frequency of 1 Hz. The pulse duration was 10 ms. Pulse trains required to drive the actuator were stored on MP3, permitting an unrestrained mobility of the subjects during co-activation. Laser vibrometer measurements revealed that the amplitude of the actuator in these experiments was 10 to 20 microns [10], but 100 microns in others [6].



To demonstrate the specific, Hebbian nature of the co-activation protocol, i.e., the requirement for temporally synchronous stimulation, we compared the effects of co-activation with a so-called single-site stimulation, where only a small "point-like" skin area was stimulated (Fig. 1.2). Otherwise, the stimulation frequency and duration of stimulation period were the same [4]. To apply an electrical repetitive stimulation, the pulse sequence is fed into a standard TENS device, and the electrical pulses are transmitted by adhesive surface electrodes fixed to the first and third finger-segment (cathode proximal). Depending on the protocol, the stimulation intensity was adjusted to 1.5 to 3 times the sensory threshold.

1.6.1 Assessment of tactile and sensorimotor performance

The sense of touch comprises quite diverse features. From an operational point of view with regard to an investigation of the sense of touch, one needs to break down the performance and functions related to touch into measurable variables. In our studies, we have referred to the idea of a hierarchy of tasks and task complexities, which differ in the involvement of proprioception and motor functions, and in the amount of cognitive demand.

In most studies we have used tactile acuity as a parameter describing the quality of tactile perception. There are many ways to measure and quantify fine spatial discrimination such as letter recognition, gap detection or 2-point discrimination. While in the past we have routinely used a modified 2-point discrimination test [4-6,11], we in some cases also applied the so-called grating-orientation task (GOT).

Guiding arguments for selecting 2-point discrimination as a simple and basic measure of tactile perception included a test that was easy to implement and simple to use. In addition, as we were interested in somatosensory cortical reorganization, the test should address properties of tactile information processing with little confound from cognitive contributions such as imagery, mental rotation, or cross-modal resources. Furthermore, the underlying mechanism should be interpretable in terms of cortical processing to allow computational modeling.

To obtain information of possible changes of tactile perception beyond acuity, we also applied other tests. The measurement of fine-touch sensitivity with von Frey filaments (Semmes-Weinstein), for instance, measured the touch threshold. In another approach, so-called mislocalization test fingers of the hand are stimulated near the threshold, thus evoking localization errors, i.e., a neighboring finger other than the stimulated one is incorrectly perceived as being stimulated.

A cognitively more demanding task is the ability to recognize objects by their haptic impression. We used groups of unfamiliar cubic objects made from common LEGO™ bricks, which had to be explored by haptic perception only thus providing information about haptic object recognition abilities [11,12]. To assess the dexterity and fine-motor performance of the hand and finger, a pegboard test was employed [12]. Moreover, we performed multiple-choice reaction time measurements in a finger selection visuo-tactile task to evaluate tactile reaction times.

1.6.2 Evaluation of cortical changes

To measure cortical effects of passive stimulation, several approaches were put forward. First, multi-site EEG recordings, so-called mappings of somatosensory evoked potentials (SSEP), were utilized [5]. Subsequently, the source of cortical activity following sensory stimulation was reconstructed by modeling it as a single current dipole. Electric source reconstruction was performed for the so-called N20-component (negativity at 20 ms over primary somatosensory cortex) of the evoked potentials recorded after electrical stimulation of the index finger. Another technique involved functional magnetic resonance imaging (fMRI) [4]. When performing fMRI, the BOLD (blood-oxygen-level-dependent) signal is measured, which utilizes the close relation between energy metabolism and neural activation. In both cases, we were interested in mapping out the location and extent of the finger representation before and after passive stimulation.

More recently, facilitatory and inhibitory effects on cortical excitability have been investigated by recording evoked potentials following paired-pulse stimulation techniques [13]. The paired-pulse behavior is characterized by the fact that the second response is significantly suppressed at short interstimulus intervals (ISIs), but approaches the first response more and more with increasing ISIs. To assess the excitability changes, we applied a paired-pulse protocol consisting of paired electrical stimulation of the median nerve with an interstimulus interval (ISI) of 30 ms in combination with recordings of the somatosensory evoked potentials. Peak-to-peak amplitudes of the N20/P25 response component generated in S1 were measured and compared before and after repetitive stimulation. The paired pulse behavior was expressed as a ratio (A2/A1) of the second (A2) to the first response (A1).

[10] Dinse HR, et al. "Tactile coactivation resets age-related decline of human tactile discrimination" *Annals of Neurology* 2006;60:88–94.
[11] Dinse HR, et al. "Improving human haptic performance in normal and impaired human populations through unattended activation-based learning" *Transactions on Applied Perception* 2005;2:71–88.
[12] Kalisch T, et al. "Repetitive electric stimulation for several weeks elicits enduring improvement of sensorimotor performance in seniors" *Neural Plasticity* 2010;69053.
[13] Hoeffken O, et al. "Sustained increase of somatosensory cortex excitability by tactile coactivation studied by paired median nerve stimulation in humans correlates with perceptual gain" *The Journal of Physiology* 2007;584:463–471.

1.6.3 Experimental set-up

A typical experiment consists of several components. First, a baseline assessment of perceptual and/or sensorimotor performance is carried out. Second, the repetitive stimulation protocol is applied to a single finger or all fingers, and in the case of evaluating cortical changes, SEP or BOLD recordings are performed. Subsequently, a second assessment serves to quantify the efficacy of the stimulation-induced learning processes, and additional follow-up tests are required to gain information about stability and duration of stimulation-induced alterations.

1.7 Main effects of tactile and electrical coactivation in healthy young subjects

1.7.1 Stimulation-induced alterations of perception and somatosensory cortical organization

The basic effects of coactivation on tactile acuity are illustrated in Figure 3. We can see 2-point discrimination thresholds for 35 subjects plotted versus successive sessions [14]. Except for the first session, all subjects showed a remarkably stable and reliable baseline of performance with little scatter. After coactivation, all subjects without exception improved their acuity as indicated by a lowering of thresholds by approximately 15 %. Retesting after 24 hours revealed a restoration of the initial baseline performance. These results were the first demonstrating that it is possible to evoke an improvement of the sense of touch in human subjects after solely a few hours of passive, albeit temporally patterned, stimulation.

To study the relation between learning-induced changes in behavior and individual changes in brain organization, we assessed perceptual performance and cortical reorganization in the same subject through a combination of psychophysical tests and non-invasive imaging. Using neuroimaging and electric source localization we demonstrated that coactivation led to an increase in the size of the cortical representation specific to the co-activated finger. The observed expansion of the cortical maps can be regarded as a recruitment of processing resources. Under the assumption that changes of cortical maps representing the co-activated index finger reflect changes in cortical processing causally related to the processing of tactile information, we hypothesized that cortical alterations should correlate with the changes in individual performance. Linear correlation analysis revealed significant relations between the coactivation-induced cortical map changes and the parallel improvement in two-point discrimination ability (Fig. 1.3). Accordingly, a small gain in spatial discrimination abilities was associated with small changes in cortical maps. On the other hand, the subjects demonstrating a large cortical reorganization also had the lowest threshold [4,5]. A similar result was obtained for changes of cortical excitability. Following coactivation, paired-pulse suppression was reduced, and the amount of suppression was positively correlated with the individual gain in performance [13].

Combined, these data revealed that coactivation results in a selective reorganization in primary somatosensory cortical areas. Furthermore, they showed that poor learners, i.e., individuals having gained little by passive stimulation, were characterized by small changes in cortical processing. These observations were taken as an argument that differences in size effect typically observed across individuals may reflect true dissimilarities in individual brain reorganization.

To demonstrate the Hebbian nature of the co-activation protocol, we compared the effects of co-activation with a so-called single-site stimulation, where only a small "point-like" skin area was stimulated. Stimulating the finger with only a single site did not give rise to any changes in acuity thresholds. In addition, the comparison of pre and post single-site stimulation fMRI sessions revealed no significant alterations in BOLD signals, thus confirming that single-site stimulation had no effect, whether psychophysically or cortically [4]. These results imply that a Hebbian "co"-activation is crucial for the induction of the effects, and point to the requirement of spatial co-operative processes.

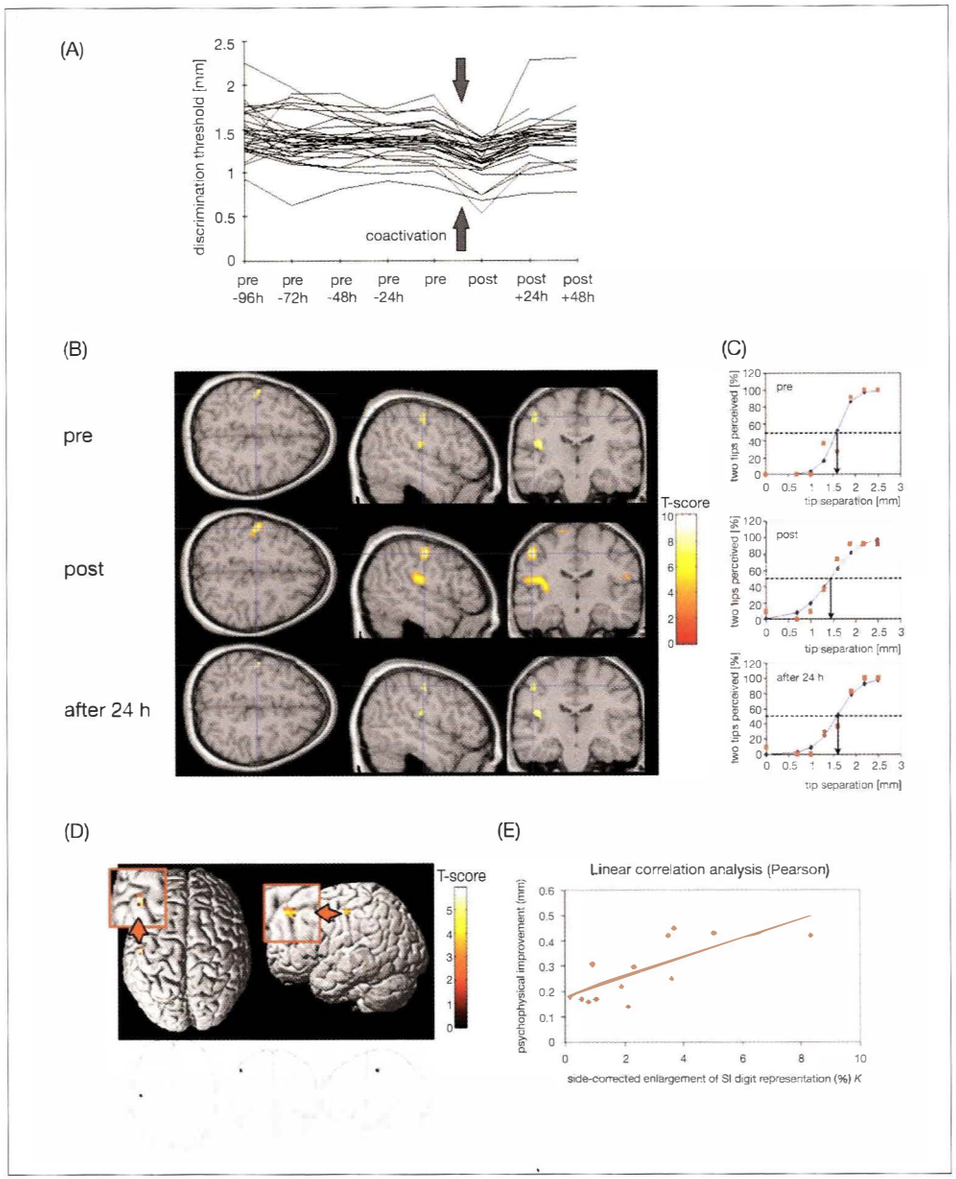
1.7.2 Pharmacological basis of coactivation

Cellular studies suggest that there might be only a few basic mechanisms controlling synaptic transmission; in particular, the N-methyl-D-aspartate (NMDA) receptor has been implicated in synaptic plasticity. In order to demonstrate that coactivation is mediated by established plasticity mechanisms we tested its dependency on NMDA receptor activation. To scrutinize the apparently ubiquitous role of NMDA receptors for passive stimulation processes we used memantine, a substance known to selectively block NMDA receptors [5]. A single dose of memantine was found to eliminate coactivation-induced learning, both psychophysically and cortically (Fig. 1.4) providing strong evidence for the NMDA-R dependence of coactivation-induced learning.

While there are many approaches to block plastic processes pharmacologically, less is known about drugs capable of enhancing cortical plasticity. According to *in-vitro* experiments, alterations of the synaptic efficacy can be modulated by adrenergic agents, thereby gating synaptic plasticity. Also, adrenergic substances such as amphetamine have been shown to aid the recovery from stroke and aphasia. We therefore used single doses of amphetamine [5] to test its modulatory role in learning processes evoked by the coactivation protocol. The application of a single dose of amphetamine resulted in practically a doubling of both the normally observed improvement of tactile acuity and of cortical reorganization [5]. These findings indicate that the processes underlying coactivation are further controlled through neuromodulatory systems.

[14] Godde B, et al. "Associative pairing of tactile stimulation induces somatosensory cortical reorganization in rats and humans" *Neuroreport* 1996;8:281–285.

Figure 1.3
Effects of repetitive sensory stimulation on tactile acuity and cortical reorganization.
(A) Tactile two-point discrimination thresholds of the index finger of the right hand in 35 subjects. Thresholds were measured five days before and immediately after coactivation (arrows) and on two subsequent days. In all subjects, thresholds were reduced immediately after coactivation but returned to control values one day after termination of the stimulation. Reprinted with permission from: Godde B, et al., *Neuroreport* 1996;8:281–285.
(B) BOLD signals detected pre, post, and 24 hrs after coactivation in the contralateral SI in the postcentral gyrus and in the contralateral SII in the parietal operculum above the Sylvian fissure. Activations are projected on an axial (left), saggital (middle), and coronar (right) T1- weighted, normalized MRI slice. Comparing pre- with postcoactivation fMRI sessions revealed enlarged activation and increased BOLD signal intensity in SI and SII contralateral to the coactivated IF. These changes of BOLD signal characteristics recovered 24 hrs after coactivation was applied.
(C) Psychometric functions illustrating the coactivation-induced improvement of discrimination threshold for the subject shown in (B). Correct responses in percent →



(red squares) are plotted as a function of the separation distance together with the results of a logistic regression line (blue with blue diamonds). 50% levels of correct responses are shown as well as thresholds. Top, precondition before coactivation; middle, postcondition, immediately after coactivation; bottom, recovery after 24 hrs. After coactivation there occurred a distinct shift in the psychometric functions toward lower separation distances, which recovered to preconditions 24 hrs later.
(D) Relationship between changes in BOLD signals and coactivation-induced changes of two-point discrimination thresholds. Results revealed a significant correlation between perceptual and cortical changes within SI on the postcentral gyrus (see also magnified detail). In contrast, no activated clusters were found within SII.
(E) Linear correlation analysis between perceptual and cortical changes in SI (Pearson) corroborated these findings. The corresponding number of activated voxels per cluster K = ((rightpost - rightpre) - (leftpost - leftpre))/rightpre, was correlated with coactivation-induced changes in psychophysical thresholds ($r = 0.744$; $p = 0.002$).
Parts B – E are reprinted with permission from: Pleger B, et al., *Neuron* 2003;40:643–653

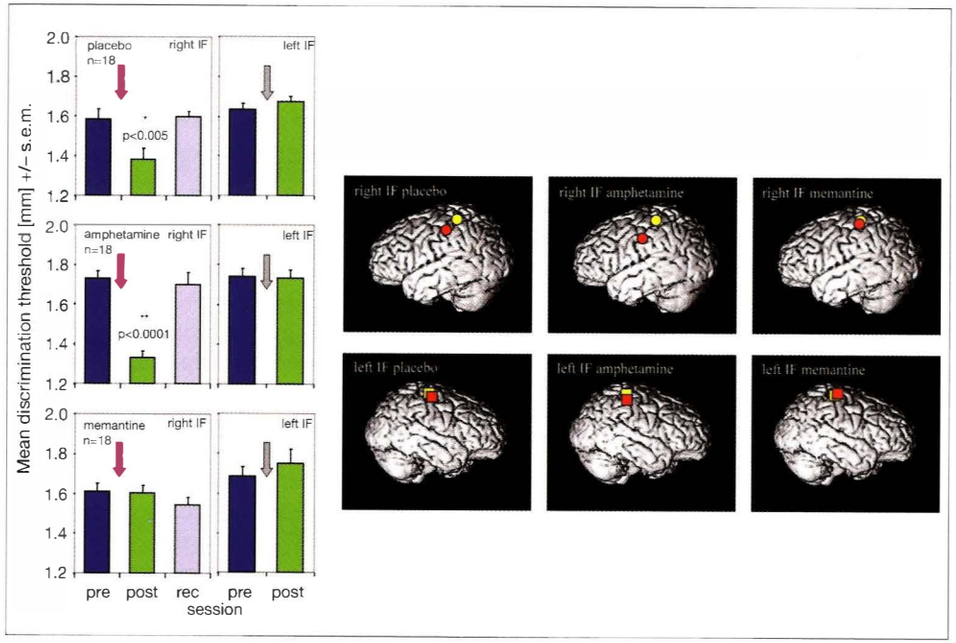


Figure 1.4
Left: Pharmacological modulation of coactivation effects on discrimination thresholds (mean +- SEM). The 3-hour coactivation episode applied to the tip of the right IF is indicated by pink arrows for the right hand and gray arrows for the left hand. For each group, discrimination thresholds obtained for the test finger (right IF) are shown pre- and postcoactivation and 24 hrs after coactivation (rec). For the control finger (left IF, which was not coactivated), thresholds are shown for the pre- and post-coactivation conditions. The general lack of effects for the control finger indicates the finger-specificity of the coactivation protocol (in the placebo group) and a lack of unspecific side effects (in the drug groups).
Right: Schematic projection of the average locations of the single equivalent N20-dipoles of the index finger pre- (yellow symbols) and post- (red symbols) coactivation onto a 3D reconstructed individual MRI dataset. Note the coactivation-induced shift towards the lateral and inferior aspects of the postcentral gyrus in the placebo group, which is nearly doubled in the amphetamine group, but blocked under memantine, an NMDA-receptor blocker. Comparable effects are lacking in the non-coactivated hemisphere (bottom row). Reprinted with permission from: Dinse HR, et al., *Science* 2003b;301: 91–94.

Combined, our data show that coactivation-induced perceptual learning and associated cortical changes are regulated by basic mechanisms known to mediate and modulate synaptic plasticity. Moreover, our data demonstrate that the use of specific drugs leads to coactivation that can be further amplified, thus opening the possibility for a systematic investigation of "neuroenhancement" of learning processes in human individuals.

1.7.3 Musicians

The potential of repetitive stimulation is not limited to young adult subjects, but has been applied in musicians whose tactile performance is already enhanced. Therefore, the question was whether there was room for further improvement. Despite the superior baseline performance, coactivation resulted in an even higher gain of tactile acuity. While the baseline performance correlated well with the duration of daily piano practicing, the coactivation-induced improvement was related to the number of years of extensive piano playing. These findings imply stronger capacities for plastic reorganization in pianists, and point to enhanced learning abilities, which have been discussed in respect to meta-plasticity [15].

1.8 Protocols utilizing temporal pattern of stimulation

According to cellular studies, long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission are the leading candidates for activity-dependent changes in the strength of synaptic connections. Typically, to induce LTP in brain slices, high-frequency stimulation (HFS, 10 Hz and higher) is utilized, while LTD can be reliably evoked by low-frequency stimulation (LFS) around 1 Hz.

Passive stimulation has a unique property of offering a complete control of its timing and spatio-temporal spacing. Thus, passive stimulation is an ideal tool for systematically exploring the requirements for the induction of perceptual and cortical changes through synaptic plasticity protocols. For this reason, we translated stimulation protocols that are used in brain slices into tactile high or low frequency stimulation (tHFS and tLFS) to drive perceptual changes. tHFS consisted of pulse trains that were applied to the tip of the right index-finger with a stimulation frequency of 20 Hz using a small actuator with a diameter of 8 mm. Each train consisted of 20 single pulses of 20 Hz lasting 1s with an inter-train interval of 5s. tLFS was applied at 1 Hz with stimulus trains consisting of 1200 pulses (Fig. 1.5). The duration of tHFS and tLFS was 20 min each. It was found that 20 min of tHFS induced a lowering of tactile discrimination thresholds, indicating an improved tactile acuity, whereas LFS resulted in an impaired performance on the right, stimulated finger. Most interestingly, 24 hrs after tHFS, the

[15] Ragert P, et al. "Superior tactile performance and learning in professional pianists: Evidence for meta-plasticity in musicians" *European Journal of Neuroscience* 2004b;19:473–478.

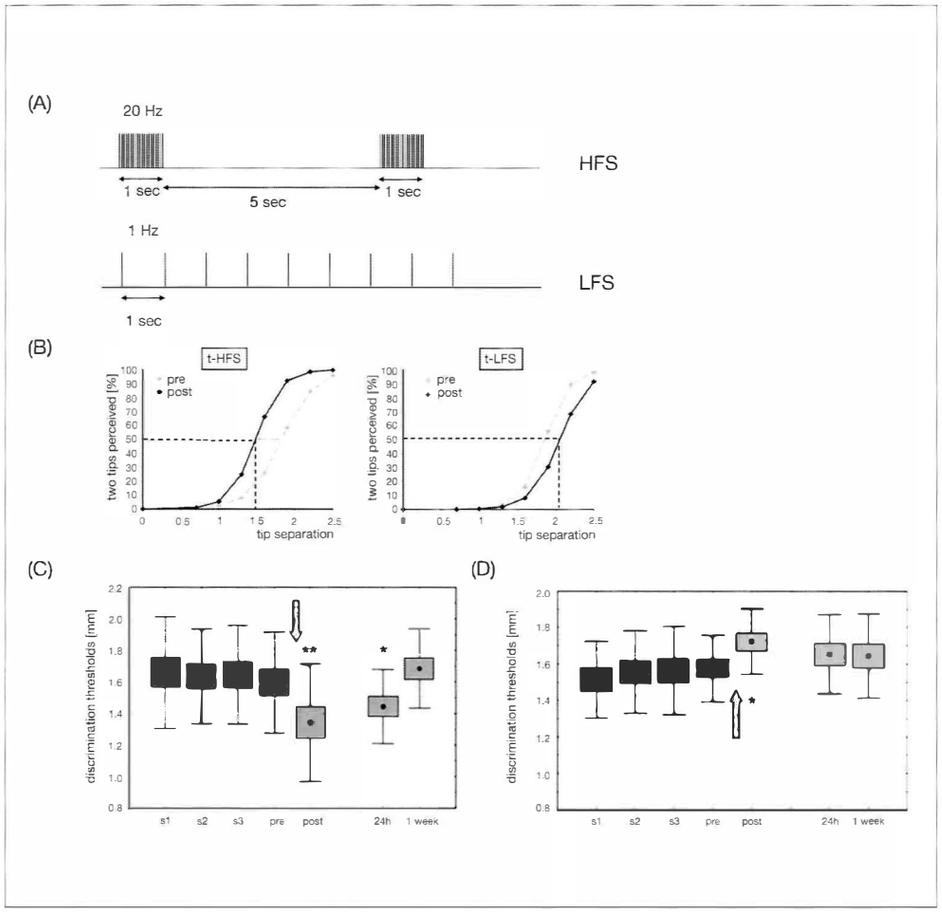


Figure 1.5
(A) Stimulation pattern used for high-frequency (HFS) and low-frequency (LFS) stimulation.
(B) Psychometric functions (regression curves) illustrating the differential effect of 20 min of HFS and LFS stimulation in two representative subjects. Correct responses in percent are plotted as a function of the separation distance. A 50% level of correct responses is indicated together with resulting thresholds (dashed horizontal and vertical lines). Dashed grey lines show pre-condition before, solid black lines post-condition immediately after HFS or LFS. After HFS, there is a distinct shift in the psychometric functions towards lower separation distances. After LFS, we found an analogous shift in the psychometric curve towards larger separations. Reprinted with permission from: Ragert, P., et al., *BMC Neuroscience* 2008;9:9-last page.
(C) Mean psychophysical effect of HFS (n = 14), (left) and LFS (n = 13) (right) on tactile discrimination thresholds of the right index finger. Dots represent mean thresholds, boxes show standard errors, and whiskers correspond to the standard deviation. Time of HFS or LFS application was 20 min each (indicated by arrow). The results are from 4 consecutive sessions before stimulation was applied. After HFS, discrimination thresholds were significantly reduced, which persisted up to 24 hrs after termination of HFS. One week after HFS, tactile discrimination thresholds recovered to baseline conditions. In contrast, after LFS, discrimination thresholds were significantly increased, indicating an impaired tactile performance. 24 hrs after termination of LFS, discrimination thresholds recovered to baseline conditions. Reassessment of thresholds 1 week later revealed a stable performance. Reprinted with permission from: Ragert, P., et al., *BMC Neuroscience* 2008;9:9-last page.

spatial 2-point discrimination thresholds were still lowered in comparison to the baseline (Fig. 1.5). In contrast, 24 hrs after tLFS, the discrimination thresholds had recovered to baseline conditions [6]. These results indicate that brief stimulation protocols resembling those used in cellular LTP and LTD studies for only 20 min can induce meaningful and persistent frequency-dependent bidirectional alterations of tactile human discrimination behaviors and of the cortical excitability.

1.9 Wide range of effects of passive stimulation on tactile perception and sensorimotor performance

A central aspect of passive stimulation is that sensorimotor improvement is not induced through training of a particular task, but through modification of synaptic efficacy in neural networks. Therefore, we hypothesized that passive stimulation remodels the entire way of neural processing related to tactile, haptic and sensorimotor information processing. Such a hypothesis predicts that passive stimulation not only affects acuity thresholds but also that passive stimulation influences almost all tasks involving tactile, haptic and sensorimotor processing. We found an improved performance for tactile acuity (as measured by 2-point or grating discrimination), frequency discrimination, dot-pattern discrimination, haptic object recognition, reaction times and decision-making, as well as sensorimotor performance such as peg-board performance. Interestingly, localization tasks became impaired (cf. next section), and a parameter typically not affected by repetitive stimulation was the touch threshold. We therefore argued that touch thresholds predominantly reflect peripheral factors such as mechanoreceptor density and mechanoreceptor composition, which remain unaffected by cortical plasticity processes.

Task interdependencies

Does the enhancement of a particular ability occur at the cost of others? In other words, is there a simultaneous trade-off between abilities gained and those lost? As described above, when subjects improve their tactile discrimination abilities (i.e., perceive two closely spaced stimuli as separate), this develops at the cost of localization performance (i.e., accurately telling the position of a stimulus on the skin). A similar observation has been made in blind Braille readers, who improve acuity at the cost of localization [16]. Interestingly, both the improvement of discrimination and the impairment of localization evolve without altering touch thresholds, which implies a trade-off between localization and discrimination on the one hand, but the independence of both parameters from the touch threshold on the other hand (see also section 1.14.1). Another example involves haptic exploration, where haptic recognition is poorly associated

[16] Sterr A, et al. "Changed perceptions in Braille readers" *Nature* 1998;391:134–135.

with tactile acuity. These findings demonstrate that there exist processing modes that are independent from each other, implying that cortical processing is highly modular and task-specific.

1.10 Effects of repetitive stimulation protocols in the visual domain: Improving visual-guided behavior

So far, we have demonstrated a substantial enhancement of perception and behavior through passive stimulation for the tactile domain. On the other hand, massive and enduring plastic changes have been described for all modalities, confirming the contemporary view that all cortical areas are modifiable beyond the critical sensitive periods. Nevertheless, the somatosensory cortex appears to differ from its visual counterpart in the readiness of inducibility, and in the magnitude, stability, and time course of changes.

We therefore adopted protocols consisting of intermittent high-frequency (LTP-like) or low-frequency (LTD-like) stimulation to the visual domain to explore the properties of modifiability of a visual guided behavior in human individuals. As a marker for induced alterations of visual perception and behavior we used a change detection task, in which two features, i.e., orientation and luminance, competed [9]. In all cases, the subjects had to report luminance changes. Under these conditions, luminance became the relevant (target) feature, with orientation being the irrelevant feature. This design allowed a specific interference since either the relevant or the irrelevant features could be used for enhancement or suppression through the passive stimulation protocols.

In order to apply LTP-like and LTD-like stimulation, participants were exposed to visual high-frequency (intermittent 20 Hz for 5 sec, interburst interval 5 sec) or low frequency (1 Hz) stimulation for 40 minutes. The LTP-like protocol using luminance (relevant feature) improved the subjects' ability to detect luminance changes, whereas LTD-like stimulation impaired their performance. On the other hand, the LTP-like exposure of the irrelevant orientation reduced the capabilities for luminance detection, while LTD-like orientation stimulation resulted in an improvement. Most notably, LTP-like effects were present for at least 10 days, while LTD-like effects were shorter-lasting [9].

Our data demonstrate that a pure exposure to protocols, which are known to modify synaptic efficacy and effectively induce bidirectional changes in human tactile perception, also efficiently altered the visual guided behavior in humans in a long-lasting manner. More importantly, the impact on the behavior depended not only on the stimulation frequency, but similarly on whether the relevant or irrelevant features were employed for the stimulation. Thus, depending on task constraints, complementary learning mechanisms induced equivalent net effects on a behavioral level, which expands the potential of fundamental learning processes in the control of human behavior. These studies confirm the universal approach of passive stimulation as a means to augment cognition and behavior independent of sensory modalities, however, more

studies are required to unravel similarities and differences between effects observed in the tactile and visual domain.

1.11 Role of attention and conscious awareness

Our experiments demonstrated that an improvement in tactile perception occurred even when subjects performed their daily routines during passive stimulation. We therefore proposed that passive stimulation operates without the involvement of attention or reinforcement [4,5]. The term "unattended activation-based learning" was coined to characterize the independence of passive learning from attentional processes [11]. However, the possibility remained that focused attention might have an influence by further enhancing changes in tactile performance and cortical plasticity. We therefore took advantage of the short duration required to drive significant changes through passive stimulation in order to systematically evaluate the impact of attention and conscious awareness on improvements in tactile performance induced by passive stimulation.

In order to drive perceptual improvements, we applied the tactile high-frequency stimulation (tHFS) protocol described above [6] for 30 min to the right index finger. Three groups were formed, differing with respect to the attentional load and attentional focus. The subjects of group 1 were asked to focus their attention on the stimuli of the tHFS protocol. They were furthermore requested to note when the regular sequence of trains was interrupted by a missing train, which happened only a few times, and had no effect on the outcome of the stimulation procedure itself. The subjects of group 2 had to perform an auditory oddball paradigm, thereby pulling attention away from the stimulated finger, and directing it towards a different sensory modality. The subjects of group 3 were asked to carry out a mental calculation task, constituted of consecutively subtracting a 4 digit number by 7. This was done to impose a severe attentional load on the subjects with the goal to exhaust attentional resources. After tHFS, irrespective of the experimental condition, the tactile acuity of all three groups was improved by approximately the same magnitude.

Furthermore, we measured the paired pulse suppression according to the description above. Similarly, we found comparable degrees of enhanced cortical excitability in all three groups. These findings indicate that neither the amount of attention paid to the tactile stimuli nor the degree of distraction influenced the outcome of repetitive stimulation, thus suggesting that selective attention is not essential and/or beneficial for the efficacy of tHFS.

Earlier evidence against passive learning

Researchers agree that attention plays an essential role in perceptual learning and experience-related plasticity. Following this view, numerous studies have shown that learning appears to depend on whether subjects focus their attention to specific features. Research of this type has been taken as support for the hypothesis that subjects need to be aware of and focus their attention on a stimulus feature for that feature to be learned. In fact, a close inspection of the literature reveals that much of the apparent evidence pointing at the role of attention in perceptual learning has been presented as evidence against passive learning [17]. Of particular interest were experiments providing evidence that perceptual learning does not necessarily depend on selective attention. Subjects were repeatedly presented with a background motion signal so weak that its direction was invisible, thus rendering it irrelevant to the central task. However, the repetitive exposure improved the performance, specifically for the direction of the exposed motion when tested in a subsequent suprathreshold test [18].

On the other hand, there exist reports according to which a prolonged "passive" stimulation was insufficient for driving plastic changes. In studies of auditory learning, the pairing of sensory stimulation with its electrical counterpart of the Nucleus basalis has been shown to result in rapid and selective reorganization of cortical maps [1]. However, control experiments have revealed that sensory stimulation alone, without NB, was ineffective. Similarly, passive exposure to tactile stimulation in monkeys made to perform an auditory discrimination task had no effect on their tactile discrimination abilities [19]. These apparent discrepancies with our data from passive stimulation can be settled in the light of the experiments using single site stimulation only [4,6]. Under such conditions (i.e., a small field or single site stimulation), no effects were observed, neither with regard to discrimination abilities nor cortical processing. Accordingly, in order to be effective, sensory stimulation must incorporate principles such as spatial (coactivation) and/or temporal (high-frequency) summation (cf. Sect. 1.14).

1.12 Passive stimulation as an intervention to augment perception and sensorimotor behavior

1.12.1 Healthy elderly individuals

Aging exerts a major reorganization and remodeling at all levels of brain structure and function, which is paralleled by a progressive decline of mental and physical abilities. On the other hand, it is now well-documented that age-related changes are not a simple reflection of degenerative processes, but rather a complex mix of plastic, adaptive, and compensatory mechanisms, suggesting that brain plasticity is operational into old age. Considering the current demographic changes in many civilizations, there is an urgent need for measures permitting an independent lifestyle into old age.

[17] Seitz A, Dinse HR. "A common framework for perceptual learning" *Current Opinion in Neurobiology* 2007;17:148–153.
[18] Watanabe T, et al. "Perceptual learning without perception" *Nature* 2001;413:844–848.
[19] Recanzone GH, et al. "Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency discrimination task" *Journal of Neurophysiology* 1992;67:1031–1056.

Consequently, strategies such as training, exercising, practicing, and stimulation making use of neuroplasticity principles are essential to maintain health and functional independence throughout the lifespan.

Sensory processes gradually lose efficiency in old age. Glasses and hearing aids are standard devices for elderly people. Yet, in contrast to vision and hearing, the dramatic age-related deterioration of the sense of touch goes mostly unnoticed as there are no conditions, such as reading newspapers or obtaining a driver's license, which might reveal this impairment. As a result, the sense of touch and its vital role for coping with activities of daily living is widely underestimated. Elderly individuals progressively adapt to the loss of high-level tactile performance and learn to compensate by developing behavioral strategies, such as relying more on visual control to overcome the decrement in the sense of touch.

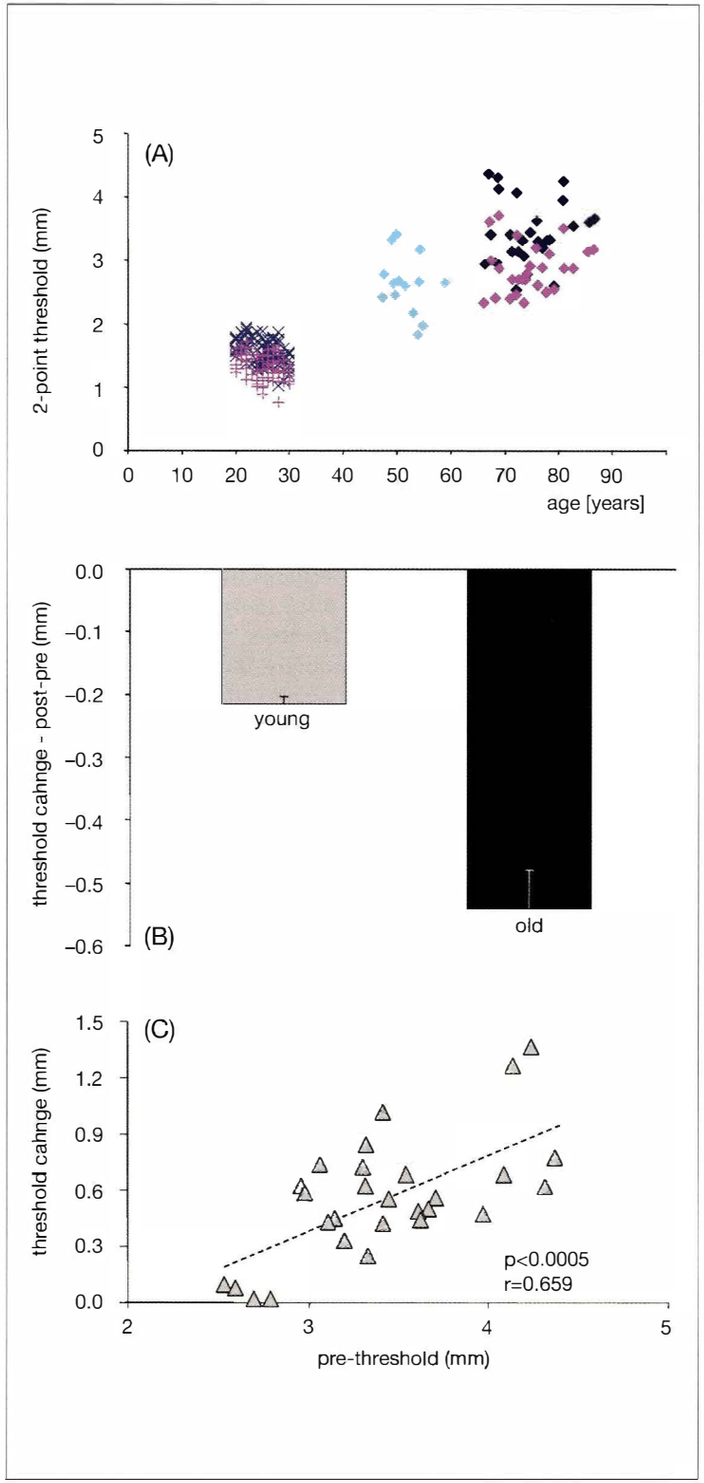
At a perceptual level, regardless of the technique used, researchers agree that tactile acuity is significantly reduced during aging. Interestingly, tactile acuity declines much more vigorously in certain areas of the body than in others. According to one study [20], the deterioration of acuity in the big toe averaged about 400 % between young and elderly subjects (aged 65 to 87 years) as compared to an average decline of 130 % observed in the fingertip.

We have therefore used tactile coactivation as an alternative intervention to interfere with the age-related impairment of tactile perception and asked whether passive stimulation is similarly affective in elderly individuals [10]. When the same coactivation protocol used in previous studies with young individuals was applied to aged participants, we found that they responded differently. Prior to coactivation, the discrimination threshold of individuals under 60 was better than for those who were 60 and older. After coactivation, this difference disappeared and the tactile acuity of the older individuals matched the average performance of participants aged between 47 and 59 (Fig. 1.6). These results demonstrated that the age-related decline of perception is not irreversible, but can be ameliorated by specific stimulation protocols [10]. Interestingly, the participants who had the highest thresholds before the start of the study showed the largest improvement, while participants with low thresholds (better acuity) presented only a limited improvement. This finding suggests that elderly individuals with the largest tactile impairment benefited most from the treatment.

Repetitive stimulation in elderly individuals was also shown to restore to a considerable extent haptic and sensorimotor performance. It was of particular interest to find that a repeated application of repetitive stimulation over several weeks resulted in a stabilization of the tactile improvement for 2 weeks or more, thereby providing a way to make the beneficial effects of passive stimulation more long-lasting [12].

[20] Stevens JC, Choo KK. "Spatial Acuity of the Body Surface over the Life Span" *Somatosensory and Motor Research* 1996;13:153–166.

Figure 1.6
(A) Tactile two-point discrimination thresholds of the tip of the right index finger as a function of age (a total of 120 subjects). After coactivation (violet symbols), thresholds of the coactivated subjects (young control group and elderly group) were significantly reduced. The coactivation-induced improvement in the group aged from 66 to 86 was several times stronger in magnitude compared with the younger subjects. As a result, after coactivation, the thresholds of the elderly resembled those found in the subjects aged from 47 to 55. (B) Comparison of the extent of coactivation-induced lowering of discrimination thresholds between young and elderly subjects. The figure shows average precoactivation - postactivation differences in threshold and standard error. (C) Linear correlation analysis (Pearson's) between thresholds on the right index finger under pre-conditions and the magnitude of discrimination threshold changes (postcoactivation – precoactivation). We found a significant correlation indicating that pre-thresholds determine the amount of coactivation-induced improvement. Reprinted with permission from: Dinse HR, et al., *Annals of Neurology* 2006;60:88–94.



Our findings demonstrate that despite the accumulation of degenerative processes during aging, the typical decline in tactile performance is not inevitable; rather, it is preventable and subject to restoration by adequate stimulation protocols. Preserving a sufficient tactile acuity in old age is an important prerequisite for the maintenance of independent living. Consequently, these approaches may be beneficial in maintaining everyday sensorimotor competence in the elderly.

1.12.2 Stroke patients

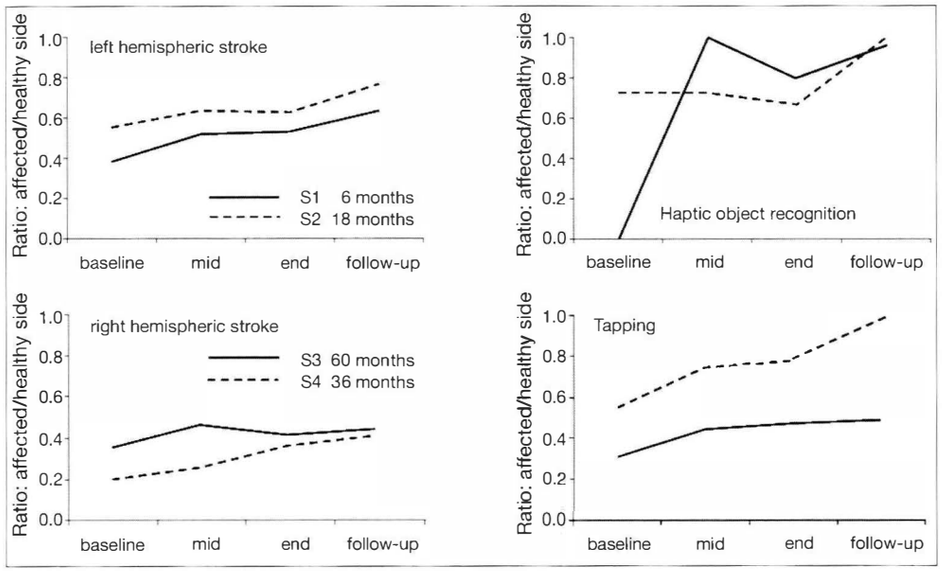
Sensorimotor impairment resulting from stroke can have extensive physical, psychological, financial and social implications despite available neurorehabilitative treatments. Intact somatosensory input is not only crucial for tactile perception but also for sensorimotor performance. The loss of sensory abilities of the more involved upper extremity, particularly the hands, further complicates the individual's ability to use their hands for functional tasks, and this in spite of a possible recovery of motor functions.

Generally, following stroke, a rehabilitation based on neuroplasticity mechanisms utilizes task-specific training and massed practice to drive reorganization and improve sensorimotor functions [21]. However, since a large number of patients suffer from restricted mobility, the development of additional and alternative approaches able to supplement, enhance, or even replace conventional training procedures would be advantageous. Therefore, in recent years, numerous attempts have been made to search for additional rehabilitative techniques [7,8,11]. However, different studies use quite different protocols, making comparability difficult. For example, the analysis of a large number of investigations revealed that the duration of stimulation varied between 20 min and 2 h per day, whereas the duration of the whole intervention ranged from a single application to 8 weeks of repeated treatment. In many cases, the stimulation sequences used repetitive square pulses in a frequency range of 1 Hz to 100 Hz, with higher frequencies applied more often.

Based on our previous studies in healthy individuals, which demonstrated substantial improvements of tactile, haptic and sensorimotor performance, we assumed that passive stimulation protocols should evoke positive effects in stroke patients. A high-frequency electrical stimulation was thus employed on all fingers of the affected hand. The rationale was to induce plastic processes within and around those brain areas having become dysfunctional from stroke. Furthermore, as a repeated application of passive stimulation had been shown to enhance both the magnitude and stability

[21] Taub E, et al. "New treatments in neurorehabilitation founded on basic research" *Nature Reviews Neuroscience* 2002;3:228–236.

Figure 1.7
Time course of sensorimotor performance of the upper extremity (hand/arm) in chronic stroke patients (left or right media infarct). The time following the infarct is indicated. The figure also shows the ratio of performance between the affected and unaffected side. A ratio of 1 indicates an identical performance on both sides. Left: Performance averaged across all tasks tested including touch threshold, discrimination threshold, tapping, haptic object recognition, pegboard, and 4 tasks form the Wolf Motor Function Test, at 4 time points baseline, mid treatment, post treatment, and 4 weeks later (follow-up). Right: Changes in performance for selected tasks. Depending on the time and side of infarct, repetitive stimulation resulted in differential strong improvement. It should be noted that individual tasks can show above-average improvement. Reprinted with permission from: Smith PS, et al., *Archives of Physical Medicine and Rehabilitation* 2009;90:2108-2111.



of effects [12], long-term applications of passive stimulation protocols were utilized over several weeks.

In subacute stroke patients, a daily application of repetitive stimulation over 4 weeks induced an improvement with regard to basic tactile tasks, such as touch threshold and tactile acuity, as well as for the sensorimotor performance. These improvements were preserved even after 3 months of follow-up [22]. In another study on chronic stroke patients (for which the average post stroke time was 30 months), the individuals were treated with repetitive stimulation during 4 days a week for 6 weeks. A significant improvement of sensory and motor performance of the affected hand resulted (Fig. 1.7). Remarkably, after a follow-up period of 6 weeks, the same magnitude of improved sensorimotor performance could be observed [23].

[22] Dinse HR, et al. "Repetitive sensory stimulation training in stroke" *European Journal of Neurology* 2008a;15:400.
[23] Smith PS, et al. "Effects of repetitive electrical stimulation to treat sensory loss in persons poststroke" *Archives of Physical Medicine and Rehabilitation* 2009;90:2108–2111.

As noted earlier, the particular advantage of repetitive stimulation is its passive nature, which does not require an active participation or attention of the subjects. Therefore, repetitive stimulation can be applied in parallel to other occupations, substantially facilitating the implementation of the intervention and rendering it more acceptable to the individual. We therefore initiated single case studies, where we treated individuals in which the stroke dated back more than 13 years. In all cases, repetitive stimulation was applied in the subjects' homes on a regular basis (5 days a week, during 45 to 60 minutes per day) using computer-controlled devices that monitored the times and durations of the stimulation sessions. Up to now, we have treated individual patients for more than 2 years, and in almost all cases we have observed beneficial effects with regard to the tactile and sensorimotor behavior. However, in certain cases, the improvements developed only after months of stimulation, and continued to increase on a time scale of months (Fig. 1.8).

Our data showed that repetitive stimulation-induced effects in stroke patients can be quite long-lasting when applied on a regular schedule over several weeks. Furthermore, positive effects in long-term chronic patients might emerge only after months of intervention. For these reasons, we believe that the effectiveness of repetitive sensory stimulation in improving tactile and sensorimotor performance, together with the advantage of using it under everyday conditions by laypeople in their homes, make repetitive sensory stimulation-based principles prime candidates for interventions in impaired populations (Fig. 1.8).

1.13 Time course, stability and magnitude of effects

Little is known about the stability and maintenance of tactile performance in healthy individuals under everyday-life conditions. Data from human subjects whose arms and fingers were immobilized due to their having to wear a cast revealed that tactile acuity dropped significantly within 1 to 2 weeks of immobilization [24]. These findings indicate that performance is not stable without maintained practice and use.

When passive stimulation was applied in a single session, although it depended on the protocol used, beneficial effects persisted up to 24 hours or more (for a detailed discussion of stability of effects see [11,12]). Accordingly, when a high-frequency protocol lasting 30 minutes was utilized, the induced improvement outweighed the time needed for induction by a factor of almost 50.

A crucial prerequisite for employing passive stimulation as a tool in intervention is the long-term persistence of induced perceptual and behavioral enhancements. A repeated application of repetitive stimulation in elderly individuals on a bi-weekly basis for 4 weeks resulted in prolonged effects where the tactile acuity

[24] Lissek S, et al. "Immobilization impairs tactile perception and shrinks somatosensory cortical maps" *Current Biology* 2009;19:837–842.

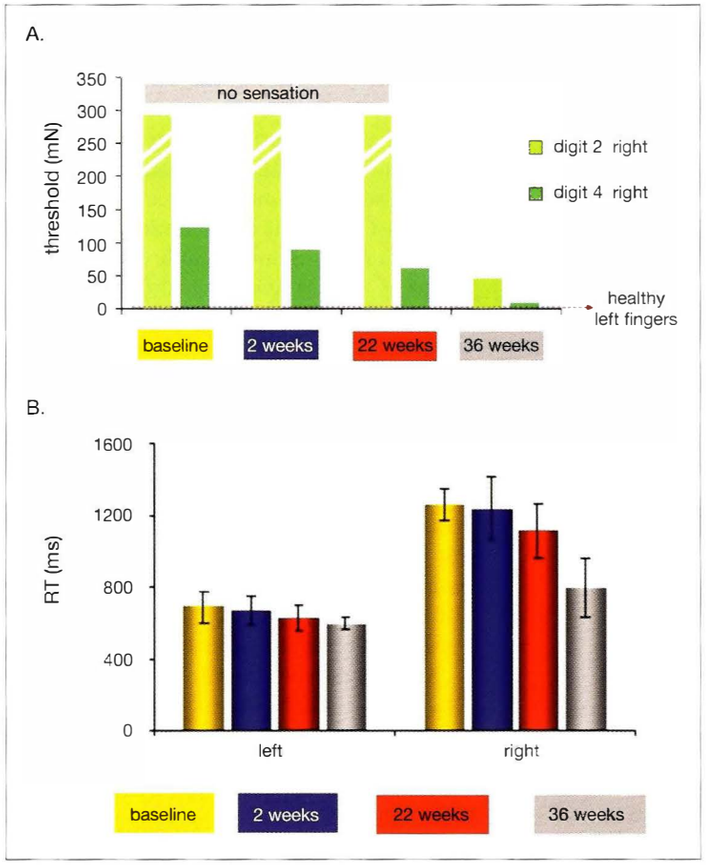


Figure 1.8
Effects of long-term treatment in a chronic stroke patient (post stroke time: 13 years). The baseline gives the performance prior to treatment, the number of weeks indicates the duration of a regular schedule of repetitive stimulation (5 days a week, for 60 minutes a day, intermittent high-frequency electrical stimulation of all fingers of the affected hand according to [6]).
A. Touch threshold measured on digits 2 and 4 of the affected hand. The average performance of the fingers of the unaffected hand is given by the red arrow.
B. Multiple-choice reaction times. The figure shows mean values obtained from all fingers of the affected and unaffected hand. One should note a substantial improvement which restored sensation and performance even in cases of complete lack of touch sensation (A) after prolonged periods of stimulation.

recovered to the baseline within 2 weeks, while the gains in haptic and motor performance were preserved for at least another two [12]. When stroke patients were treated with repetitive stimulation for several weeks on a daily basis, follow-up measurements revealed a full preservation of beneficial effects up to 3 months following the termination of the stimulation. Thus, a long-term, repeated application of passive stimulation is highly effective to drive sustained alterations.

As a rule, the improvement of acuity after passive stimulation was in the range of 10 to 20 %. Given these numbers, it is not clear *a priori* whether such an improvement represents a major advance bearing relevance for everyday life. In other words, we do not know how far training-based improvements of sensory skills are comparable in magnitude to those evoked by short periods of passive stimulation. For this reason, acuity changes induced by various protocols of passive stimulation, applied for minutes to hours, were compared with acuity changes found in musicians or in blind individuals as a result of long-year training. Surprisingly, acuity changes for pianists, violinists, or blind individuals were almost identical to those obtained after short periods of passive stimulation [11].

1.14 Views on mechanisms

According to our current view, passive stimulation drives synaptic plasticity processes in the cortical areas representing the stimulated sites. The observed expansion of the cortical maps can be regarded as a recruitment of processing resources. The effectiveness of passive stimulation appears to result from the fact that the impact of sensory stimulation must be sufficient to drive the neural system past the point of a learning threshold [17]. Factors that "optimize" sensory inputs include high-frequency or burst-like stimulations as well as heavy schedules of stimulation (i.e., a large number of sensory stimuli). These boost responses to sensory stimulation that are normally insufficient to drive learning past this threshold (Fig. 1.9). Under conventional training conditions, factors such as reinforcement, motivation, reward and attention – which are all brought into action through neuromodulatory systems such as the dopaminergic (reward) or the cholinergic (attention) system – appear to play a permissive role. Interestingly, as described above (cf. Sect. 1.7.2), the efficacy of passive stimulation is also controlled by neuromodulatory systems [5]. For example, applying amphetamine enhances effects of passive stimulation, while the application of scopolamine, which blocks the cholinergic system, suppresses passive stimulation-induced effects [25].

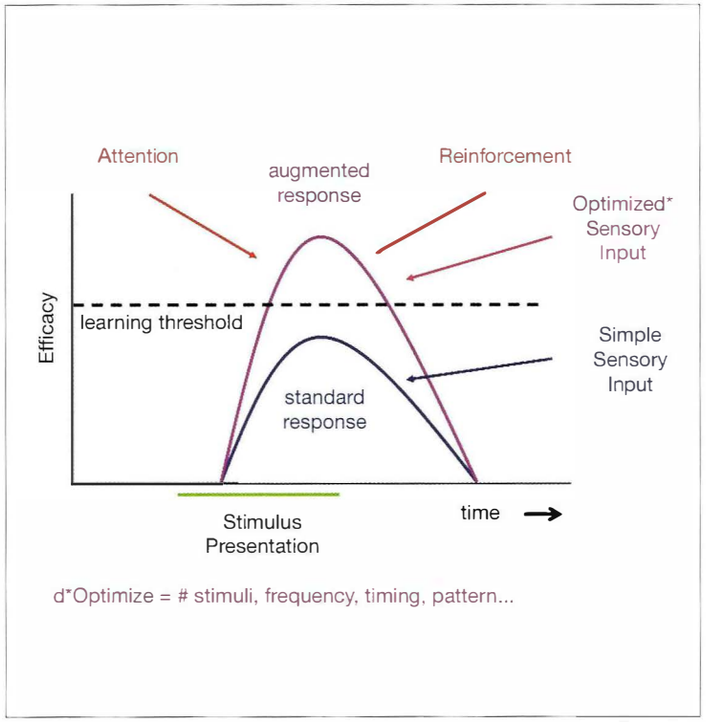
Most notably, the effects induced by passive stimulation do not leave the cortical networks in a disorganized state, but on the contrary lead to the emergence of a different, yet organized and meaningful functioning as indicated by the improvement of perception and behavior. What remains to be clarified are the underlying properties and processes that enable cortical networks to become stabilized into new organized states, mediating a better performance after being modified through passive stimulation lacking behavioral or contextual information.

1.14.1 Modeling passive stimulation

To understand the tactile spatial discrimination performance and its alterations during stimulation-induced learning we established a computational model using a mean-field approach. Cortical population activity within cortical maps is modeled with a Mexican hat interaction of short-range excitation and longer-range inhibition. In the model, stimulation at a single site evokes single peaks of activation coding for the subjective experience of a single stimulus, while simultaneous stimulation at two sites (like in 2-point discrimination experiments) evokes 2 peaks corresponding to the percept of 2 stimuli. In contrast, localization refers to the ability to precisely read out the position of the peak of population activation.

[25] Bliem B, et al. "Cholinergic gating of improvement of tactile acuity induced by peripheral tactile stimulation" *Neuroscience Letters* 2008;434:129–132.

Figure 1.9
Conceptual framework depicting factors for gate learning. The key assumption is that for sensory stimulation to be sufficient, it must drive the neural system past the point of a learning threshold. Responses evoked by simple sensory stimulation fail to induce learning. Factors such as attention or reinforcement have important permissive roles and play a critical part in training and practice-based learning conditions. On the other hand, all factors that relate to the timing and temporal structure of stimulation, such as high-frequency or burst-like pattern, alternatively optimize simple inputs by driving them across the learning threshold. Reprinted with permission from: Seitz A, Dinse HR., *Current Opinion in Neurobiology* 2007;17:148-153.



Lateral inhibition reduces coexisting, ongoing activation present at other locations of the cortical population. As coexisting activation is necessary for bimodal activation profiles coding for the perception of two sites, a strong lateral inhibition deteriorates the discrimination performance. On the other hand, a lateral inhibition suppresses the influence of noisy fluctuations of activation leading to a subsequent reduction in the variance of the read-out of the peak position. Thus, spatial discrimination and localization are oppositely affected by lateral interaction [26].

To model the effects of passive stimulation, we reduced the amount of lateral inhibition. This is in line with empirical findings pointing at a decreased intracortical inhibition. As a result, less lateral inhibition in the model increases the size of the cortical representation, which is consistent with fMRI and EEG studies. For discrimination (stimulation at 2 sites), the decrease in inhibitory interaction leads to bimodal activation profiles for distances that before learning evoked only single peaks. In contrast, localization-reduced inhibition permits coexisting activation, which leads to a more powerful influence of noise, thus deteriorating localization abilities. As a result, stimulation-reduced lateral inhibition improves

[26] Dinse HR, et al. "Learning in haptic perception" (2008) Grunwald (ed) Birkhäuser, pp.165–182.

localization performance but decreases discrimination performance. These studies indicated that perceptual alterations induced by passive stimulation depend on changes of amplitude and width of lateral interaction processes [26].

1.14.2 A role of neurotrophic factors

Animal research suggests a fundamental role of brain-derived neurotrophin factors and other nerve growth factors in controlling and maintaining synaptic connections and brain plasticity. More generally, a mild stress response in cells has been advocated as a major driving force capable of up-regulating stress resistance genes and growth factors [27]. Among the factors inducing mild stress can be mentioned physical activity, cognitive challenges and sensory stimulation. It is therefore conceivable that the up-regulation of neurotrophic factors is induced by passive stimulation protocols, particularly under conditions of long-term repeated application of repetitive stimulation as is the case in the treatment of stroke patients. We therefore suggest that enhanced tactile and sensorimotor performance may arise as a consequence of increased levels of neurotrophins, which are up-regulated during stimulation, and which might act as a form of metacontrol of classical synaptic plasticity processes.

1.15 Is this "learning"?

Throughout this chapter, we have referred to the effects of passive stimulation as "learning processes". The rationales for this have involved empirical data according to which the effects of repetitive stimulation (1) depend on NMDA-receptor activation [5], thus demonstrating that the effects of passive stimulation are mediated by very basic mechanisms underlying synaptic plasticity, and (2) demonstrate a facilitation of intracortical excitability [13]. We therefore argued that the effects of passive stimulation are based on modifications of synaptic efficacy and transmission, both fundamental principles underlying "learning".

From a more general and psychological point of view, learning is defined as the acquisition of new knowledge, behaviors, skills, values, preferences or understanding, and may involve synthesizing different types of information. Human learning may occur as part of education, personal development, or training. It may be goal-oriented and may be aided by motivation. Apparently, the term "learning" is rather broadly defined, and is not restricted to the everyday-life concept of acquiring knowledge as is the case during school learning. Given such a broad definition, it is our view that the outcome of improvement observed following passive stimulation readily qualifies as learning.

[27] Mattson M. "Hormesis defined" *Ageing Research Reviews* 2008;7:1–7.

1.16 Conclusion

The data we obtained from the tactile and visual domains provide evidence that pure exposure to sensory stimulation enhances perception, behavior and cognition. However, to be efficient, stimulation must conform to requirements described for protocols specifically altering synaptic transmission and efficacy. Thus, our data indicate that the application of canonical protocols that are fundamental in regulating and controlling synaptic plasticity can be used directly to interfere with human behavior. From that, we conclude that the usage of canonical stimulation protocols might be an ultimate way to induce learning processes. The persistency of changes, the ease of application and the wide range of effects make passive stimulation an ideal tool in the targeted intervention for improving perception, behavior and cognition.

To make this feasible, it is necessary to develop stimulation devices that can be used under rigorous everyday conditions by laypeople at their homes. Conceivably, given that exposure-based learning is a relatively new development, we are only at the beginning of an area where targeted brain manipulation will offer completely new scenarios of learning, with implications that are difficult to foresee.

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