Review article

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Hubert R. Dinse[1,2] · Martin Tegenthoff[2]

[1] Neural Plasticity Lab, Institute fur Neuroinformatik, Ruhr University Bochum, Bochum, Germany

[2] Neurologische Klinik am Berufsgenossenschaftlichen Universitätsklinikum Bergmannsheil, Ruhr-University, Bochum, Germany

Evoking plasticity through sensory stimulation: Implications for learning and rehabilitation

It is generally agreed that processes allowing modification of synaptic efficacy are the neural substrates for learning. Synaptic plasticity mechanisms either facilitate or suppress transmission at synapses to alter communication between nerve cells. Long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission are leading candidate models allowing investigation of activity-dependent changes in synaptic connection strength [26]. Typically, high-frequency stimulation is used to induce LTP in brain slices, whereas LTD can be reliably evoked by low-frequency stimulation [3, 23, 24].

However, the lack of adequate input stimuli for the induction of LTP and LTD in humans has hindered direct evaluation of the impact of such protocols on human behaviour. Which role plays LTP or LTD in human learning? Are these relevant processes at all to understand what happens during everyday learning? Synaptic plasticity studies use temporally specific stimulation protocols to induce long-lasting changes in synaptic transmission, but the implications of this requirement for temporally specific protocols in everyday learning remain unclear. For training- and practice-based learning to occur, sensory inputs are modified in their frequency, temporal pattern, the number of stimuli and their duration, form, size and intensity [32, 33]. But it is difficult to exactly quantify the numerous changes in input parameters that occur during training. Therefore, linking the principles of synaptic learning that induce plasticity at the cellular level to the principles at the systems level is far from straightforward.

The rationale behind repetitive sensory stimulation

An interesting alternative is offered by a reverse approach: using the broad knowledge of brain plasticity to design specific sensory stimulation protocols that allow changing brain organization and, thus, perception and behaviour. The idea is to translate protocols that induce plasticity at a cellular level into sensory stimulation protocols. This approach has the unique advantage of offering complete control of the timing and spatiotemporal allocation of the stimulation (**Fig. 1**). Moreover, this approach is not only an ideal tool for applying known protocols to humans to assess whether such protocols can affect human perception and behaviour but also a means to systematically determine the appropriate timing for the induction of perceptual and cortical changes in humans, which can result in temporal stimulation protocols that have so far not investigated in synaptic plasticity research [2, 12]. Another advantage is that the experimental designs applied in humans can be transferred one to one to animal models, which allows further investigation of pharmacological and molecular mechanisms underlying repetitive sensory stimulation effects.

Terminology

The concept of sensory stimulation protocols to induce learning has attracted substantial interest and is currently being investigated in many laboratories, however, different laboratories are using different terms to refer processes that are essentially comparable, such as "peripheral nerve stimulation" [34], "somatosensory stimulation" [5, 39], "unattended-based learning" [9], "repetitive sensory stimulation" or "high-frequency stimulation" [30]. The idea of "coactivation" emphasizes the relevance of Hebbian learning, where synchronous neural activity is instrumental to drive plastic changes. Other laboratories use the framework of "tetanic" stimulation, which is commonly used in synaptic plasticity research, or use the term "stimulus-selective response plasticity" [4, 37]. The term "exposure-based learning" has been introduced to indicate that mere exposure is sufficient to drive perceptual changes [2, 17]. As a suggestion for unification, the term "training-independent sensory learning—TISL" has been introduced for types of learning induced by synaptic plasticity protocols in human participants with the aim of changing perception and behaviour [2]. The abbreviation TISL is therefore used throughout this review. The frequently used term "passive stimulation" or "passive learning" is meant to indicate that a subject is exposed to repetitive sensory stimulation without actively attending.

Stimulation-induced alteration of tactile and sensorimotor behaviour

The sense of touch comprises diverse features. From an operational point of view, investigation of the sense of touch requires to break down performance and functions into measurable variables. It appears conceivable to refer to the idea of a hierarchy of tasks and tasks complexities, which dif-

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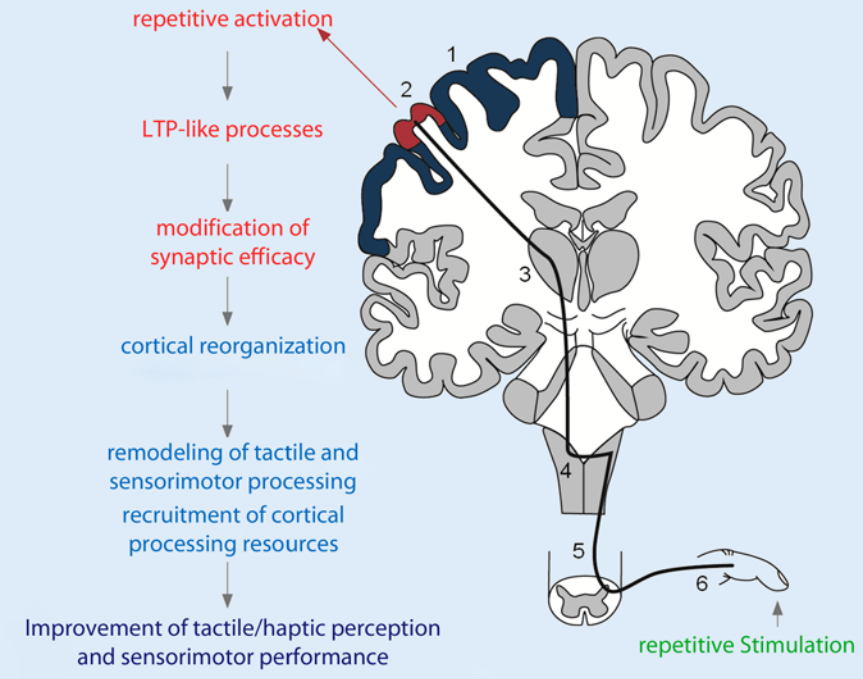

Fig. 1 ▲ Schematic illustration of the assumed chain of changes evoked by TISL. Sensory stimulation of a finger induces a cascade of functional alterations within the sensory system being targeted, leading to the induction of plastic processes which, in turn, result in behavioural/perceptual changes. *1* somatosensory cortex (*SI*), *2* finger representation in SI, *3* thalamus, *4* brain stem, *5* spinal cord, *6* mechanoreceptors in the fingers. *TISL* training-independent sensory learning

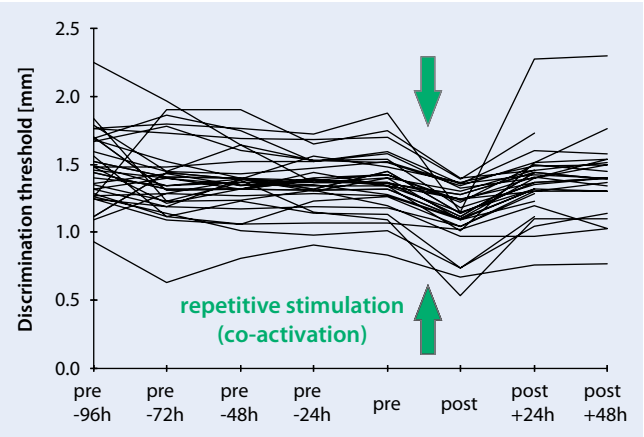

Fig. 2 ▲ Effects of coactivation, a form of TISL, on tactile acuity (tactile two-point discrimination) of the index finger of the right hand in 35 subjects (each *line* is one subject). Thresholds were measured five days before and immediately after coactivation (*arrows*) and on two subsequent days. In all subjects after coactivation, thresholds were reduced on average by approximately 15 %, but returned to control values one day after termination of stimulation. (Reprinted with permission from [15]). *TISL* Training independent learning

fer in the involvement of proprioception and motor functions, and in the amount of cognitive demand. The sense of touch is a so-called "near-sense", which requires direct contact between skin and stimulus. In contrast, vision as a far sense can be studied by presenting stimuli on a monitor, where stimuli can be easily varied. For analyzing the sense of touch, a battery of physical devices is needed, which are then brought into contact with the skin. Therefore, investigation of the sense of touch is much more difficult and time consuming. A simple and reliable marker of the quality of the sense of touch is tactile acuity, which, equivalent to visual acuity, characterizes the spatial discrimination abilities [9].

A typical experiment consists of several components: First, at baseline perceptual and/or sensorimotor performance is assessed and cortical activation parameters recorded (pre-condition). Then, the repetitive stimulation protocol is applied. Afterwards, a second assessment serves to quantify the efficacy of the stimulation-induced learning processes (post-condition), and additional follow-up tests to gain information about stability and duration of stimulation-induced alterations (recovery). Depending on the research question, the repetitive stimulation protocol can be applied to a single finger or all fingers of a hand. For application of tactile repetitive stimulation, a small mechanical actuator is taped to the tip of a finger. To apply electrical repetitive stimulation, the electrical pulses are transmitted by adhesive surface electrodes fixed to the first and third finger segment (cathode proximal).

The basic effects of TISL on tactile acuity (two-point discrimination) are illustrated in **Fig. 2**. In this experiment, the fingertip of the right index finger was repetitively stimulated with short cutaneous taps, which were transmitted to the skin via a small movable membrane. Before stimulation, all participants showed stable performance over repeated assessment sessions. After coactivation, a form of TISL, subjects without exception improved their acuity as indicated by a lowering of thresholds by approximately 15 %. Retesting after 24 h revealed restoration of initial baseline performance. These results first showed that it is possible to evoke improvement of the sense of touch in human subjects solely through a few hours of passive, but temporally patterned stimulation [15, 16].

In this experiment, an improvement of 15 % was observed—how relevant is this gain? For example, it is known that blind individuals after years of loss of eye sight, or musicians after years of practicing an instrument have much better tactile acuity, the difference compared to non-blind or non-musicians is around 20 % [9]. Accordingly, TISL protocols induce substantial alterations of

tactile perception within short periods of times.

Alteration of cortical processing

What happens during and after TISL in the brain? Is it possible to measure in humans the signatures underlying the observed changes of perception? These questions can be answered by using non-invasive neuroimaging and electroencephalogram (EEG) recordings. Important parameters to characterize cortical processing and its changes are size and extent of cortical activation, which is often interpreted as cortical maps and map reorganization. It could be shown that after TISL, which leads to improved acuity, the sensorimotor cortical regions representing the stimulated finger were increased [28, 29] (**Fig. 3**). These findings had been interpreted as a recruitment of processing resources to make processing more efficient. Under the assumption that changes of cortical maps representing the stimulated finger reflect changes in cortical processing causally related to the processing of tactile information, it was hypothesized that cortical alterations should correlate with the changes in individual performance. Linear correlation analysis revealed significant relations between the stimulation-induced cortical map changes and the parallel improvement in two-point discrimination ability (**Fig. 3**). Accordingly, little gain in spatial discrimination abilities was associated with small changes in cortical maps. On the other hand, those subjects who showed a large cortical reorganization also had lowest threshold [29].

During the last years, intracortical excitability reflecting inhibitory and excitatory processes are studied using paired-pulse stimulation techniques [21]. The so-called paired pulse behaviour is characterized by a significant suppression of the second response at short inter-stimulus intervals. Paired-pulse suppression was reduced after TISL protocols, and the amount of suppression was positively correlated with the individual gain in performance, indicating higher excitability in good learners [18].

In addition to the analysis of local processing properties, a more complete understanding of the underlying mechanisms requires investigation of global processes as provided by functional connectivity analysis. A study addressing connectivity on the basis of EEG signals recorded in sensorimotor cortical areas showed that after TISL, functional connectivity between somatosensory and motor areas was significantly enhanced [13].

The available imaging and EEG data imply that TISL results in selective reorganization of sensorimotor areas, where the amount of reorganization is related to the individual gain of perceptual abilities, with large reorganization found in good learners and vice versa. It is a common observation that the learning outcome varies substantially across individuals. The important insight from these studies is that individual learning differences were linked to individual differences in the amount of reorganization (see chapter "Prediction of learning outcome"). Furthermore, these data show that TISL does not affect isolated neural processing parameters. Instead, the entire way of neural processing appears remodelled, which includes size and amount of activation, intracortical inhibition and excitation, and functional connectivity. Conceivably, all these changes in concert might mediate the broad range of perceptual and behavioural alterations (see chapter "Generalization of training-independent learning outcome").

Pharmacological mechanisms

Cellular studies suggest that there might be only a few, fundamental mechanisms that control synaptic transmission. In particular, the N-methyl-D-aspartate (NMDA) receptor has been implicated in synaptic plasticity. In order to demonstrate that TISL is mediated by basic plasticity mechanisms, its dependency on NMDA receptor activation was tested. To this aim, participants received a single dose of memantine, a substance known to block selectively NMDA receptors [27]. In this placebo-controlled study, it was observed that memantine eliminated the TISL-induced learning, both psychophysically and cortically (**Fig. 4**) providing strong evidence for the NMDA-R dependence of TISL-induced learning [7].

Another crucial player is gamma-aminobutyric acid (GABA), which plays an important role in the maintenance of the balance of excitation and inhibition. GABA is therefore assumed to be critically involved in stabilizing ongoing processing as well as learning mechanisms. In humans, the role of GABA can be investigated through application of drugs that contain GABA agonists (lorazepam). After a single dose of lorazepam before TISL, the typically observed improvement of tactile acuity was completely blocked [8]. These studies support the idea that TISL induces synaptic plasticity processes that are controlled

Abstract

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H.R. Dinse · M. Tegenthoff

Evoking plasticity through sensory stimulation: Implications for learning and rehabilitation

Abstract

The gold standard for improving sensory, motor and or cognitive abilities is long-term training and practicing. Recent work, however, suggests that intensive training may not be necessary. Improved performance can be effectively acquired by a complementary approach in which the learning occurs in response to mere exposure to repetitive sensory stimulation. Such training-independent sensory learning (TISL), which has been intensively studied in the somatosensory system, induces in humans lasting changes in perception and neural processing, without any explicit task training. It has been suggested that the effectiveness of this form of learning stems from the fact that the stimulation protocols used are optimized to alter synaptic transmission and efficacy. TISL provides novel ways to investigate in humans the relation between learning processes and underlying cellular and molecular mechanisms, and to explore alternative strategies for intervention and therapy.

Keywords

Plasticity · Somatosensory systems · Perceptual learning · Therapy and intervention · Aging

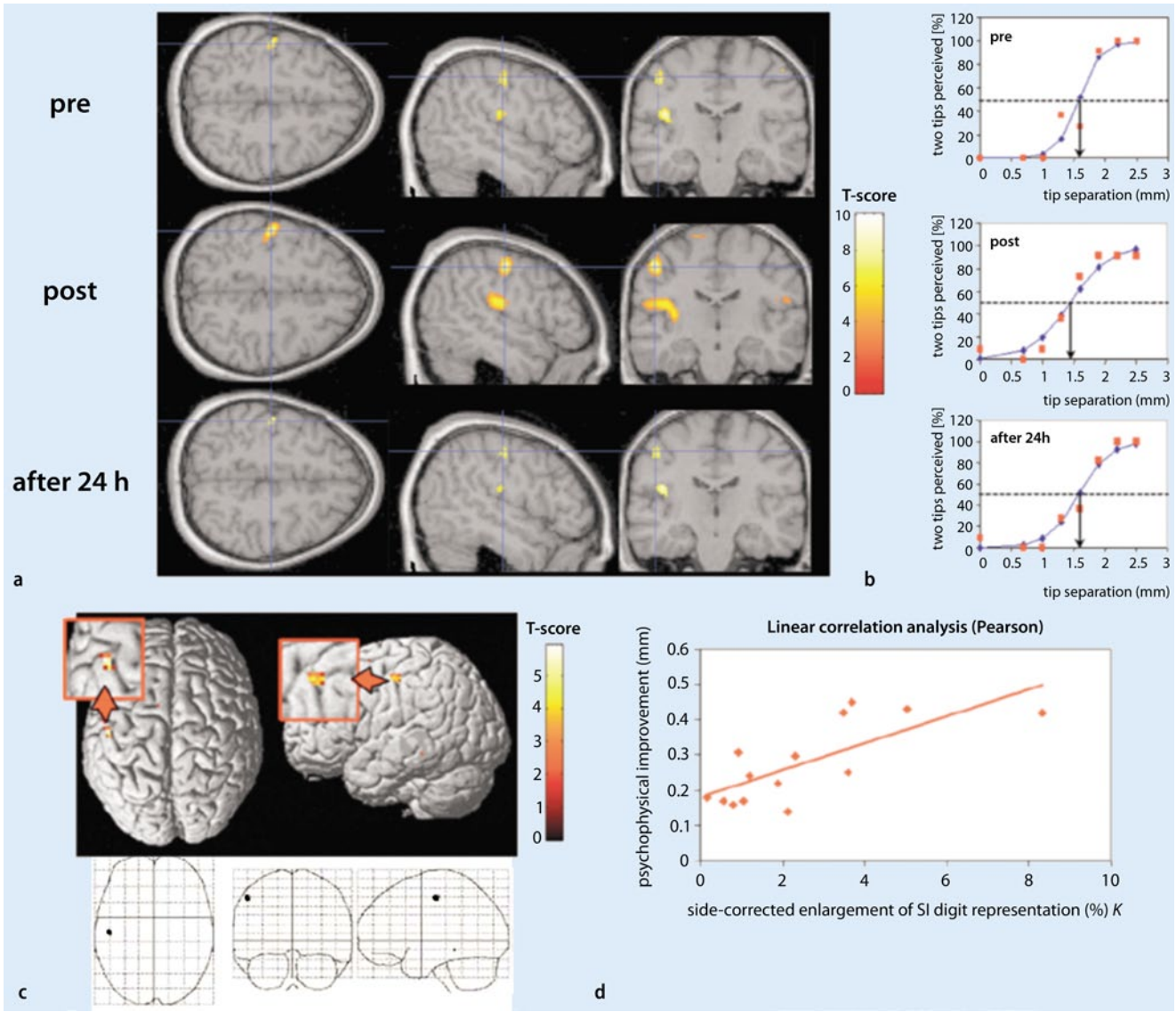

Fig. 3 ▲ Effects of coactivation on tactile acuity and associated cortical reorganization. **a** BOLD signals detected pre, post and 24 h after coactivation in the contralateral SI in the postcentral gyrus and in the contralateral SII in the parietal operculum above the Sylvian fissure. Activations are 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 h after coactivation was applied. **b** Psychometric functions illustrating the coactivation-induced improvement of discrimination threshold for the subject shown in **a**. Correct responses in percent (*red squares*) are plotted as a function of separation distance together with the results of a logistic regression line (*blue* with *blue diamonds*). Fifty percent levels of correct responses are shown as well as thresholds. *Top*, precondition before coactivation; *middle*, postcondition, immediately after coactivation; *bottom*, recovery after 24 h. After coactivation, there is a distinct shift in the psychometric functions towards lower separation distances, which recovers to preconditions 24 h later. **c** 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. **d** 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 ($r = 0.744$; $p = 0.002$). (Reprinted with permission from [29]). *MRI* magnetic resonance imaging, *fMRI* functional MRI

by glutamatergic and GABAergic receptors.

While there are many approaches to block plastic processes pharmacologically, less is known about drugs that enhance cortical plasticity. According to in-vitro experiments, alterations of synaptic efficacy can be modulated by adrenergic agents thereby gating synaptic plasticity. Therefore, single doses of amphetamine were used to test its modulatory role in learning processes evoked by TISL. Application of a single dose of amphetamine resulted in almost a doubling of both the normally observed improvement of tactile

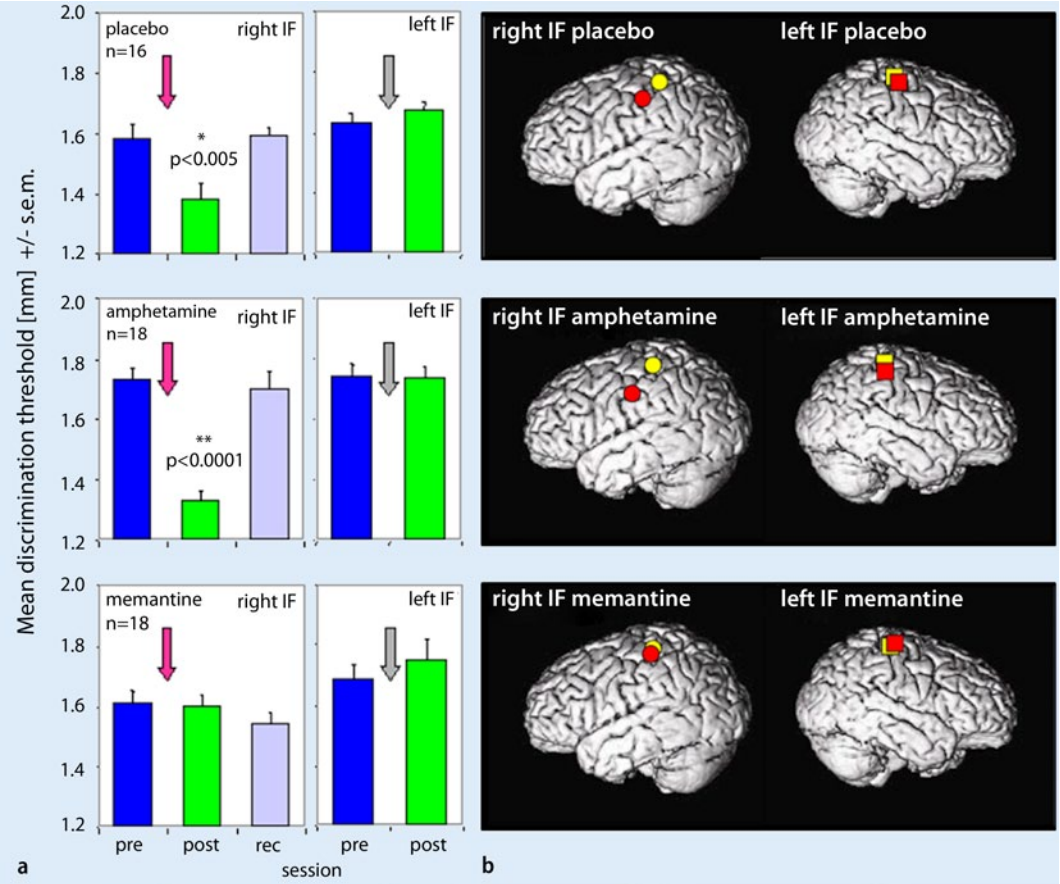

Fig. 4 ▲ Pharmacological alteration of TISL-induced perceptual and neural changes through application of memantine (NMDA-blocker) and amphetamine. **a** Pharmacological modulation of coactivation effects on discrimination thresholds (mean ± SEM). The 3-h coactivation episode applied to the tip of the 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 h after coactivation (rec). For the control finger (*left IF*, which was not coactivated), thresholds are shown for the pre- and postcoactivation 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). **b** Schematic projection of the average locations of the single equivalent N20-dipoles of the index finger pre- (*yellow symbols*) and postcoactivation (*red symbols*) 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, the NMDA-receptor blocker. Comparable effects are lacking in the not-coactivated hemisphere (*bottom row*). (Reprinted with permission from [7]). *TISL* training-independent sensory learning, *NMDA* N-methyl-D-aspartate, *MRI* magnetic resonance imaging

acuity and of cortical reorganization [7]. These findings indicate that the processes underlying TISL are further controlled and amplifiable through neuromodulatory systems.

Bidirectional changes are frequency dependent

As outlined above, LTP and LTD are leading candidate mechanisms describing activity-dependent changes in the strength of synaptic connections [6]. To explore the relevance and efficacy of these in-vitro stimulation protocols in driving perceptual changes in humans, they were translated into tactile high- and low-frequency stimulation pattern. Tactile high-frequency stimulation (tHFS) consisted of cutaneous pulse trains consisting of 20 single pulses of 20 Hz with an inter-train interval of five seconds. Low-frequency stimulation (tLFS) was applied at 1 Hz. Only 20 min of high-frequency stimulation induced a lowering of tactile discrimination thresholds, whereas low-frequency stimulation resulted in an impaired discrimination performance [30]. To show that LTP- and LTD-like tactile protocols also affect cortical processing in a reciprocal way, somatosensory evoked potential (SEP) recordings after median nerve paired-pulse stimulation were performed before and after tHFS and tLFS. While tHFS increased excitability, tLFS reduced it. These results indicate that brief stimulation protocols (< 30 min), resembling those used in cellular LTP and LTD studies, can induce bidirectional, frequency-dependent relevant and persistent alterations in tactile discrimination behaviour of humans.

Role of attention

Learning through training depends critically on attention and motivation. In case of TISL, which is believed to directly affect

synaptic plasticity mechanisms because of the temporal protocols used, factors such as attention should play a minor role. To test this hypothesis, three groups of subjects were subjected to the same TISL protocol. In group 1, subjects were asked to focus their attention on the stimuli of the TISL protocol. They were asked to note when the regular sequence of trains was interrupted by a missing train. In group 2, subjects had to perform an auditory oddball paradigm, thereby pulling attention away from the stimulated finger and directing it towards a different sensory modality. In group 3, subjects had to perform a difficult mental calculation task to exhaust attentional resources. In all three groups the learning outcome was similar, irrespective of the experimental condition, which supports the specific conditions under which learning can occur when using TISL protocols (see chapter "Training-independent learning as intervention in stroke patients").

Predicting learning outcome

It is an everyday phenomenon that there are good and bad learners, which also holds for perceptual learning under laboratory conditions. Why that is remains mostly elusive. There are many factors that can lead to poor learning: for example, impaired sensory periphery preventing inputs from getting into brain areas that learn. There can be a lack of attention, or an impairment of learning mechanisms as is the case in brain-derived neurotrophic factor (BDNF) polymorphism [20].

TISL is particularly suited to study learning variability, because attention can be excluded as a potential contributing factor. A recent EEG study used TISL to demonstrate that spontaneous EEG rhythms recorded in somatosensory cortex (mu rhythm) is another important predictor for learning. Because the somatosensory mu rhythm is in the 10 Hz range, it is also referred to as alpha rhythm. It was observed that two independent processes explained about 65 % of the learning variance: high learning, as assessed by high gains in tactile acuity, was found when a participant showed high spontaneous alpha power before TISL. In addition, high learning occurred when during TISL there was a high event-related desynchronization. These data imply that brain states are another important factor that influences learning [14]. An open question is whether the observed states represent a snapshot, or alternatively a fingerprint of the individual participant. Independent of this, the exciting practical option appears to manipulate baseline alpha power through neurofeedback to control the learning outcome.

Hand–face learning transfer

Tactile inputs arising from neighbouring skin portions are processed in the brain in neighbouring regions as well. The resulting complete body representation in somatosensory cortex is called homunculus. One prominent exception from this neighbouring-preserving mapping rule is the face–hand border, where fingers and face are located side by side although they are physically far apart. Reduction of tactile inputs following amputation or deafferentation induces perceptual changes across this border, which are explained by plastic competitive mechanisms striving for cortical territory [31]. Whether cross-border plasticity can also be induced by learning processes that rely on increase of somatosensory input remained unknown. To explore possible cross-border learning transfer, the right index finger was stimulated using a standard TISL protocol. This improved tactile perception not only at the right stimulated index finger but also at the unstimulated right cheek and upper lip. These findings demonstrate that learning-induced perceptual improvement can cross the face–hand border, suggesting that mechanisms other than competition, such as facilitation-based plasticity, might operate during learning-induced reorganization in the healthy human brain [25]. The cross-border perceptual improvements provide evidence that increasing input to a body part can positively affect touch perception at cortically close, but physically distant body parts. Further experiments are needed to clarify whether these transfer properties can be used as intervention to treat impairments in the face regions through stimulation of the fingers.

Generalization of training-independent learning outcome

Training a specific task improves performing this task. However, improvements are specific for the trained task, with little transfer to other tasks. Against the background of potential application as intervention, much research is currently devoted to overcome this "curse of specificity", so that training outcome more readily transfers in a broad range, preferentially to real-life situations.

A central aspect of TISL is that improvement of perception is not induced through task training, but through modification of synaptic transmission in neural networks. In this sense, TISL is task independent. This view predicts that TISL not only affects acuity thresholds, but the entire way of neural processing related to tactile, haptic and sensorimotor information processing. Therefore, in a series of experiments, other tactile, haptic and sensorimotor abilities were tested. In fact, after TISL, better performance was observed for tactile acuity (as measured by two-point or grating discrimination), frequency discrimination, dot-pattern discrimination, haptic object recognition, tactile reaction times and decision making, as well as sensorimotor performance such as dexterity [9, 12]. This broad-range generalization of positive effects is an important prerequisite to use TISL protocols as therapy and intervention in patients.

Training-independent learning in other sensory modalities

If it is true that the temporal properties of the TISL protocols induce directly synaptic plasticity, this should then be true for all sensory modalities, at least touch, vision and hearing. Recent studies in the visual system showed that TISL using LTP-like and LTD-like presentations of visual stimuli analogue to those used in the tactile system induced comparable changes of visual perception [2, 4, 37]. Similar effects were also demonstrated for the auditory system [1, 38], which supports the notion that TISL is a novel form of learning induction independent of sensory modality.

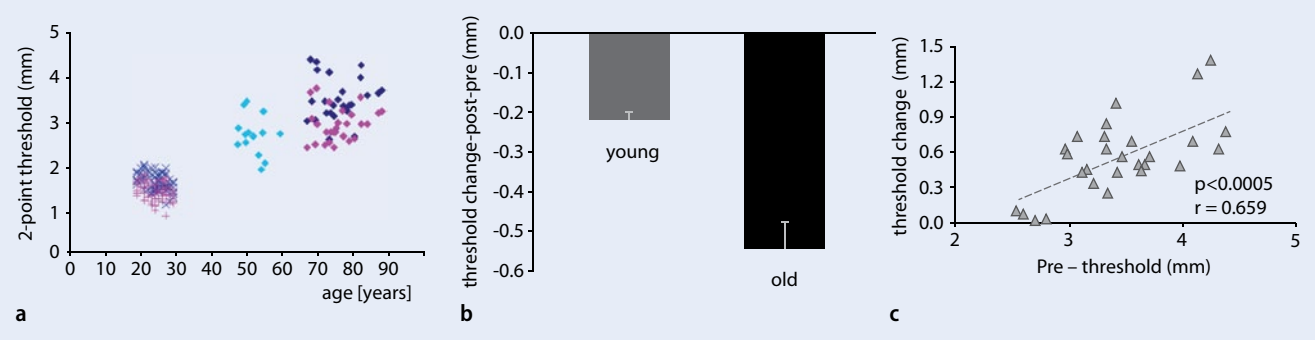

Fig. 5 ▲ Effects of TISL protocols on age-related degradation of tactile acuity of elderly participants. **a** Tactile two-point discrimination thresholds of the tip of the right index finger as a function of age (total of 120 subjects). After coactivation (*violet symbols*), thresholds of the coactivated subjects (young control group and elderly group) were significantly reduced. Coactivation-induced improvement in the group aged 66–86 years was several folds stronger in magnitude compared with the young subject. As a result, after coactivation, thresholds of the elderly resembled those found in the subjects aged 47–55 years. **b** Comparison of the amount of coactivation-induced lowering of discrimination thresholds between young and elderly. Shown are average pre–post 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 (post–pre). The significant correlation indicates that pre-thresholds determine the amount of coactivation-induced improvement, thus participants with the worst baseline performance profited most from the TISL approach. (Reprinted with permission from [10]). *TISL* Training independent learning

Efficacy of training-independent learning in elderly individuals

A first step towards a possible application of TISL as an intervention approach was studies addressing age-related decline of tactile and sensorimotor abilities in healthy elderlies [10]. Sensory processes gradually lose efficiency in old age. Glasses and hearing aids are a standard for elderly people. Yet, in contrast to vision and hearing, the dramatic age-related deterioration of the sense of touch goes mostly unnoticed. As a result, the sense of touch as well as its vital role for coping with activities of daily living (ADL) is widely underestimated. Considering the current demographic changes, there is an urgent need for measures permitting an independent lifestyle into old age. Therefore, strategies such as training, exercising, practicing and stimulation that make use of neuroplasticity principles are essential to maintain health and functional independence throughout lifespan.

To test the efficacy of TISL in elderly, a group of 65–90-year-old healthy individuals were stimulated using a coactivation-TISL protocol, and the results compared to a group of young adults and middle-aged adults 45–60 years. Prior to stimulation, the discrimination thresholds of individuals under 60 were better than those who were 60 and older. After stimulation, this difference disappeared and the tactile acuity of the older individuals matched the average performance of participants aged 45–60 years (Fig. **5**). Interestingly, participants who had the highest thresholds at baseline (pre-stimulation) showed the largest improvement, while participants with low thresholds (better acuity) had only limited improvement. This finding suggests that elderly individuals with the largest tactile impairment benefited most from the treatment [10]. These data showed that despite the accumulation of degenerative processes, the typical age-related decline of perception is not irreversible, but can be ameliorated through TISL protocols.

Training-independent learning as intervention in stroke patients

Sensorimotor impairments resulting from stroke can have extensive physical, psychological, financial and social implications despite available neurorehabilitative treatments. In particular, the loss of sensory abilities further complicates the individual's ability to use the hand for real-life situations in spite of possible recovery of motor functions. Neuroplasticity-based rehabilitation after brain injury and stroke uses task-specific training and massed practice to enforce brain plasticity to improve sensorimotor functions [36], but still a significant percentage of patients suffer from long-term invalidity [22]. Therefore, the development of additional approaches that may supplement, enhance or even replace conventional training and rehabilitation procedures is essential to make treatment feasible also over longer periods of time, taking into account both costs and compliance.

So far, the feasibility and effectiveness of TISL as intervention have been investigated in cooperation with rehabilitation centres in subacute and chronic stroke patients to improve tactile, haptic and sensorimotor functions of the upper extremities. The rational was to enforce plastic processes within and around those brain areas that became dysfunctional to facilitate recovery and compensation [12]. For stimulation, LTP-like protocols of electrical pulses were delivered to all fingers of the affected hand. Recent studies used a stimulation glove with in-build contacts on each fingertip. For objective evaluation of the impact of stroke and of the effects of TISL therapy, a broad range assessment was performed measuring tactile, motor, proprioceptive abilities and everyday life tasks.

In a group of subacute stroke patients aged 55–76 years suffering from left or right media infarct, who showed signs of severe sensoriomotor deficits of the upper

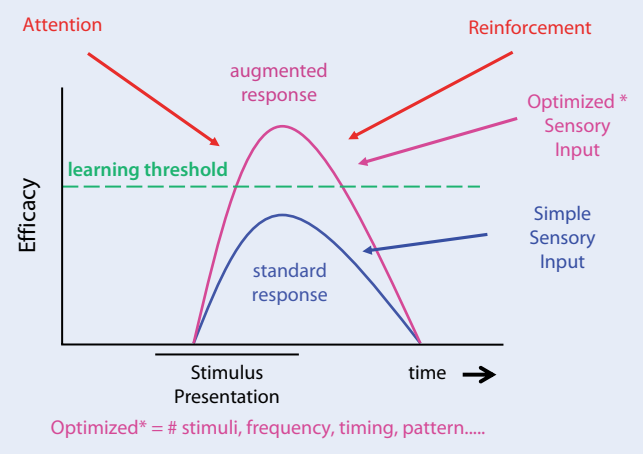

Fig. 6 ▲ Conceptual framework depicting factors that control learning. For sensory stimulation to be sufficient, it must drive the neural system past the point of a learning threshold. Responses evoked by simple sensory stimulation fail to induce learning. Factors such as attention or reinforcement play a critical permissive role 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 without requiring attention or motivation. (Reprinted with permission from [35])

extremities, repetitive stimulation was applied daily over 2 weeks (40 min per day, 5 days per week). Patients received standard physiotherapy but no specific hand/arm training. Compared to baseline, TISL induced significant improvement not only of tactile tasks, such as touch threshold and tactile acuity, but also of sensorimotor functions. Follow-up assessment after 3 months revealed preserved or even additional improvements [11].

In a randomized, placebo-controlled clinical study, a group of subacute patients (age 34–89 years) were studied to compare the effects of a combined therapy (TISL plus standard therapy including specific hand/arm training) with standard therapy and specific hand/arm training alone (treatment 2 weeks, 40 min per day, 5 days per week). Hand/arm training consisted of ergotherapy, ADL training and orthopedagogy. Compared to standard treatment, the combined therapy was superior in all domains, particularly in improving sensory and proprioceptive functions (Kattenstroth et al. in preparation).

The particular advantage of TISL is its passive nature, which does not require the active participation or attention of subjects. Therefore, TISL approaches can be applied in parallel with other techniques or other occupations, which makes this intervention very easy to implement and more acceptable to the individual. Therefore, a series of single case studies was initiated, where patients were treated with TISL protocols, in which the stroke dated back more than 10 years. In all cases, repetitive stimulation was applied at the homes on a regular basis (5 days a week, for 45–60 min per day). In all cases, beneficial effects on tactile and sensorimotor behaviour were observed, which, however, developed in some cases only after months of stimulation, and continued to increase on a time scale of months [19].

The available data show that the positive effects of TISL in subacute patients can be quite long-lasting when applied on a regular schedule over weeks. Furthermore, positive effects in long-term chronic patients might emerge only after months of intervention. For these reasons, it appears conceivable that the concept of TISL is highly suited for interventional approaches, either in combination with other rehabilitation measures, or as stand-alone approach. A particular advantage, besides low costs, is the high compliance due to using it by patients at their homes over extended periods of time, an aspect most crucial for chronic patients.

Canonical plasticity protocols explain high efficacy of TISL

The described efficiency of TISL protocols might come to a surprise. A fundamental assumption is that TISL drives rather directly synaptic plasticity processes in the cortical areas representing the stimulated sites. To explain this effectiveness, a conceptual framework had been suggested [35], where sensory learning occurs when sensory inputs pass a learning threshold (**Fig. 6**). Under normal conditions, sensory inputs are too weak to pass the learning threshold. Factors that play an important role in training-based learning are attention, reward and motivation, thereby amplifying the sensory inputs otherwise below threshold. In case of TISL, factors such as attention either play no role, or make only a small contribution. Instead, factors that "optimize" sensory inputs in case of TISL are high-frequency or burst-like features as well as heavy schedules of stimulation (i.e. large number of sensory stimuli), which boost inputs that normally are insufficient to drive learning past this learning threshold.

The validity of the TISL approach across sensory modalities supports the idea that the temporal structures and pattern used are ubiquitous. It is therefore conceivable that there are only few—canonical—conditions that effectively drive plasticity. If this is true, this will readily explain the remarkable efficacy of the TISL approach. An open question is, whether the observed dichotomy into low- and high-frequency stimulation is due to ecologic constraints where these frequencies prevailed. Alternatively, molecular and biochemical properties might have constrained the development of these temporal pattern.

Are repetitive sensory stimulation evoked changes a form of "learning"?

Throughout this chapter, TISL effects were denoted as "learning". The rationales for this were empirical data according to which the effects of TISL (1) depend on NMDA-receptor activation, thus demonstrating that the TISL effects are mediated by basic mechanisms underlying syn-

aptic plasticity, and (2) induce facilitation of intracortical excitability. Both observations characterize fundamental principles underlying "learning".

In a more general view, learning is defined as the acquisition of new knowledge, behaviours, 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, or learning a task after training. Given such a broad definition, the outcome following repetitive sensory stimulation qualifies readily as learning, as captured in the term "training independent sensory learning".

Corresponding address

H.R. Dinse
Neural Plasticity Lab, Institute fur Neuroinformatik
Ruhr University Bochum, Building NB 3
44780 Bochum
hubert.dinse@ruhr-uni-bochum.de

Hubert R. Dinse. studied biology and chemistry at the Philips-University in Marburg and the Johannes Gutenberg-University in Mainz, Germany, where he obtained his PhD. After a postdoc at the Universita di Pisa, Italy, he worked as a consultant for the Battelle-Institute in Frankfurt, Germany, and as a research fellow at the Department of Zoology at Mainz University. From 1988 to 1989 he was Visiting Professor at the University of California, San Francisco. Since 1990 he heads the Neural Plasticity Lab at the Institut for Neuroinformatik of the Ruhr-University, Bochum, Germany (www.neuralplasticitylab.de). He is Vice chair of the Department of Cognitive Systems, member of the board of directors, and senior scientist at the Department of Neurology at the University Hospital Bergmannsheil. His main research areas include learning, plasticity, and aging, tactile and visual perception, development of new learning protocols, and applied neuroplasticity for rehabilitation.

Martin Tegenthoff. Studied medicine and physics at the University of Münster. Doctoral thesis in medicine (Dr. med.). Board certification in neurology and psychiatry, specializing in pain therapy and rehabilitation medicine. Habilitation in neurology at Ruhr-University Bochum. Constitution of an interdisciplinary scientific study group for neuronal/cortical plasticity (www.ruhr-uni-bochum.de/neuroplasticity/index.html.de) with an emphasis on clinical and experimental neurophysiology and MR-neuroimaging. Since 2010, he is medical director and chair of the Department of Neurology, (Neurological Traumatology and Neurorehabilitation) University Clinic Bergmannsheil, Ruhr-University Bochum.

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