Improving Human Haptic Performance in Normal and Impaired Human Populations through Unattended Activation-Based Learning

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Human haptic performance is not fixed, but subject to major alterations through learning processes. We describe a new stimulation protocol that allows to improve haptic performance in humans in a highly systemic way through unattended activation-based learning. The so-called coactivation protocol is based upon temporal constraints of Hebbian learning where simultaneity plays a key role for the induction of plastic changes. We provide an overview about the potential of coactivation by summarizing recent findings showing that coactivation alters a broad range of basic as well as cognitively demanding types of haptic performance in parallel to cortical reorganization in somatosensory cortex. For example, coactivation applied to the tip of the index finger, or to all fingers of the dominant hand improves tactile acuity, but also haptic object recognition, and speeds up multiple-choice reaction times. Because such changes persist between 24 h and 1 week without further intervention, we interpret the underlying processes as a particular form of perceptual learning. We describe results where coactivation has been utilized for therapeutical purposes in impaired human populations, we outline new developments to optimize and extend unattended activation-based learning protocols, and we sketch the next steps necessary to apply the concept of unattended activation-based learning on a regular and reliable basis as a therapeutical tool in order to selectively interfere with impaired haptic performance.

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1. INTRODUCTION

It is common wisdom that perceptual skills improve with practice [Gibson 1953]. Consequently, haptic performance is subject to considerable modification through training, or to enhanced or reduced use [Dinse and Merzenich 2002; Recanzone 2000]. Recent studies in "perceptual learning" have shown that skill acquisition in the haptic domain is associated with selective plastic reorganizational changes in the cortical representations of the respective body part. For example, Recanzone and coworkers

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[1992] showed that tactile frequency discrimination training over several months leads to a significant reduction of frequency discrimination threshold and to an expansion of the cortical maps in somatosensory cortex that represent the used finger. On the other hand, imaging studies performed over the last years provided overwhelming evidence that extensive use and practice result in substantial changes of associated cortical representations in blind Braille readers [Pascual-Leone and Torres 1993] or string players [Elbert et al. 1995]. According to these findings, both long-term training and long-term differential use is able to modify haptic performance.

2. UNATTENDED ACTIVATION-BASED LEARNING

We have recently introduced alternative approaches to training in order to control and to improve haptic performance in humans through so-called unattended activation-based learning protocols on a very short time scale of only a few hours.

Utilizing the knowledge about brain plasticity accumulated over the last years [Buonomano and Merzenich 1998], we suggested that specific stimulation protocols can be designed through which it becomes feasible to change purposefully brain organization and thus perception and behavior.

Based on this concept, we have developed a so-called coactivation protocol, through which we can enforce localized activation pattern in the brain [Dinse et al. 2003; Godde et al. 1996, 2000; Pleger et al. 2001, 2003; Ragert et al. 2004]. Coactivation is a task-free, "passive" and therefore unattended stimulation that allows to study systematically the impact of altered input statistics on plastic capacities of cortical networks. The protocol induces perceptual improvement in parallel to cortical reorganization without invoking task information, or cognitive factors such as attention, reinforcement, or behavioral information [Dinse et al. 2003; Godde et al. 1996, 2000; Pleger et al. 2001, 2003; Ragert et al. 2004]. Coactivation follows closely the idea of Hebbian learning [Hebb 1949]: Synchronous neural activity, which is regarded instrumental to drive plastic changes, is generated by the simultaneous tactile "co-stimulation." Conceivably, coactivation modifies synaptic efficacy between and within the cortical neuron pool representing the stimulated skin sites thereby altering cortical maps and associated perceptual performance.

In the following, we describe how coactivation is applied, we summarize recent findings obtained with coactivation, we describe an alternative approach utilizing repetitive transcranial magnetic stimulation, and we outline further technical and scientific developments in the field of unattended activation-based learning.

3. COACTIVATION

To apply coactivation, a small device consisting of a solenoid with a diameter of 8 mm was taped to the tip of the right index finger (IF) (Figure 1). The device allows stimulation of the skin portions underneath thereby coactivating the receptive fields within this area. Coactivation-stimuli are drawn from a Poisson process at interstimulus intervals between 100 to 3000 ms (cf. Figure 1(D)) to prevent habituation; average stimulation frequency is 1 Hz, and the duration of each pulse is 10 ms. The pulse trains required to drive the solenoid were recorded on tape and are played back via portable tape recorders allowing unrestrained mobility of the subjects during coactivation. Subjects are instructed not to attend the stimulation. In fact, all subjects resumed their normal day's work. Coactivation stimuli are applied at suprathreshold intensities. Typical duration of coactivation is 3 h, see for more details Godde et al. [1996, 2000], Pleger et al. [2001, 2003], Dinse et al. [2003], and Ragert et al. [2004].

3.1 Experimental Schedule and Design

A typical experiment consists of two different components: First, the measurement of haptic performance as a marker of the efficacy of learning processes induced by the coactivation protocol. As a

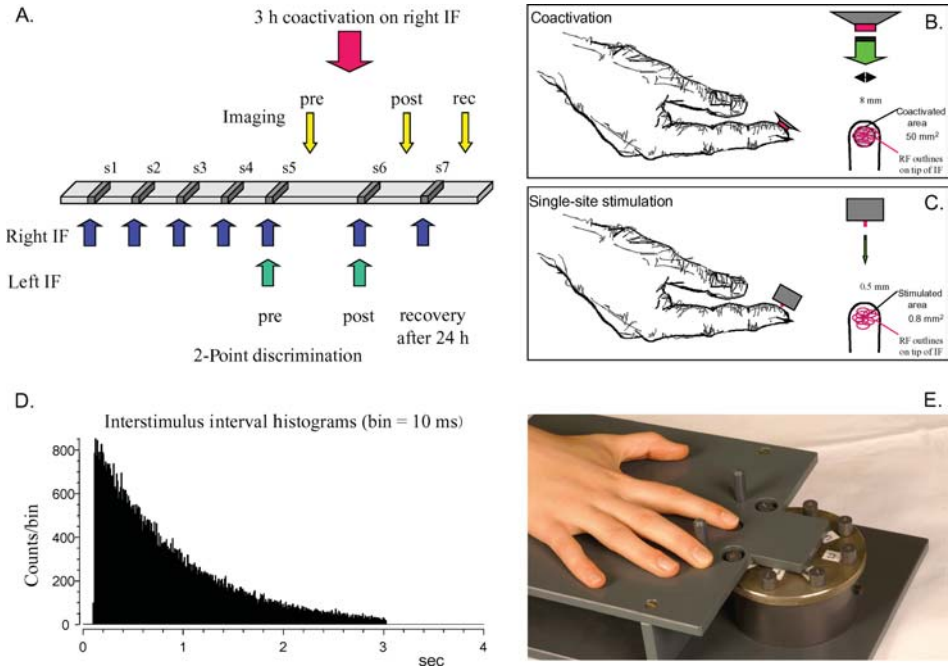

Fig. 1. (A) Experimental design: Sessions 1–5 (s1–s5) served to create a stable discrimination performance for the right index finger (IF). The left IF serving as control is only tested at session s5 (precoactivation) and after coactivation (session s6, post). After s5, preimaging is performed, then coactivation of the right IF is applied for 3 h. After the termination of coactivation and after the completion of session 6, postimaging is repeated. The 7th session (determination of two-point discrimination thresholds and imaging) was performed to assess the recovery of the coactivation-induced effect. In the case that imaging sessions are required (yellow arrows), pre, post, and recovery sessions are intermingled as indicated. (B) Application of coactivation: A small solenoid with a diameter of 8 mm was mounted on the tip of the right IF to coactivate the receptive fields representing the skin portion under the solenoid (50 mm^2). (C) Control protocol. Application of a so-called single-site stimulation: A small device consisting of only one tiny stimulator (tip diameter 0.5 mm) was mounted on the tip of the right IF to stimulate a single "point" (0.8 mm^2) on the skin. Duration of stimulation was also 3 h. The schedule was the same as described in (A) for coactivation; however, no recovery sessions were performed. Also, frequency and duration of pulses were as described for coactivation (see Pleger et al. [2003] for statistical analysis of the data). Reprinted with permission from *Neuron* [Pleger et al. 2003]. (D) Coactivation stimuli were drawn from a Poisson process to prevent habituation (ISIs truncated $<$100 ms and $>$3000 ms). (E) Device used to measure tactile acuity based on spatial two-point discrimination thresholds.

parameter, we mostly used spatial two-point discrimination thresholds on the tip of the left and right index fingers (IF), see Section 4. for other haptic parameters. Second, the coactivation on the tip of the right IF for a period of 3 h as a tool to induce perceptual learning. For details of the testing procedure see Godde et al. [1996, 2000], Pleger et al. [2001, 2003], Dinse et al. [2003], and Ragert et al. [2004]. In brief, to obtain a stable base line of performance, we tested the subjects on five consecutive sessions over several days on the right IF (Figure 1(A)). In the 5th session, the threshold of the left IF was additionally measured. Previous studies showed that the effect of task familiarization was transferred to the IF of the left hand. As a rule, the IF of the right hand was used for coactivation. In contrast to the initial task familiarization, the coactivation effect imposed on the right IF has been shown not to generalize to the IF of the left hand [Dinse et al. 2003; Godde et al. 1996, 2000; Pleger et al. 2001, 2003; Ragert et al. 2004]. Because of this locality, we used the IF of the left hand as a control and for the assessment of possible unspecific side-effects of coactivation. After applying coactivation, the effect is assessed in the 6th session directly after termination of coactivation. Stability and recovery of the

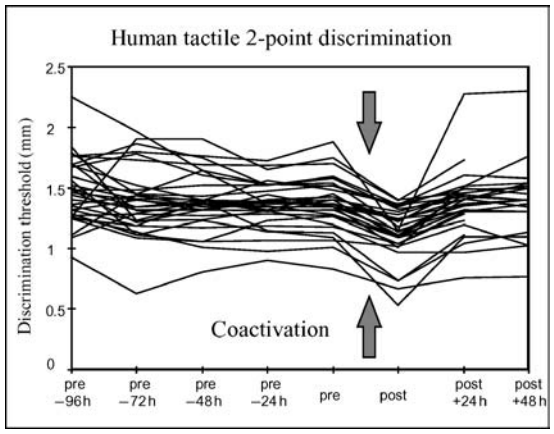

Fig. 2. Tactile two-point discrimination thresholds of the index finger of the right hand as measured in a two-alternative forced-choice discrimination experiment in 35 right-handed human subjects. Thresholds were measured five days before and immediately after coactivation (arrows) and on two subsequent days. In all subjects, thresholds were reduced immediately after coactivation but returned to control values one day after coactivation. Reprinted with permission from *Neuroreport* [Godde et al. 1996].

coactivation effects are assessed in the 7th session 24 h after coactivation. Imaging sessions (pre, post, recovery) to measure cortical representations of the IF were intermingled after sessions 5, 6, and 7 (cf. Figure 1).

Tactile two-point discrimination thresholds of the tip of the IFs were assessed using the method of constant stimuli as described previously [Dinse et al. 2003; Godde et al. 1996, 2000; Pleger et al. 2001, 2003; Ragert et al. 2004]. Seven pairs of needles (diameter 200 μm) separated by 0.7, 1.0, 1.3, 1.6, 1.9, 2.2, and 2.5 mm were used (in the studies of elderly subjects, distances up to 7 mm were used). In addition, zero distance was tested with a single needle as a control for false alarms. No feedback was given. To accomplish a rather uniform and standardized type of testing, we used a custom-made device (Figure 1E). Each distance of the needles was tested 10 times in randomized order resulting in 80 single trials per session. The subject had to decide immediately if he had the sensation of one or two tips by answering "one" or "two." The summed responses were plotted against distance as a psychometric function for absolute threshold, fitted by a binary logistic regression. Threshold was taken from the fit at the distance where 50% correct responses was reached.

3.2 Basic Effects of Coactivation

3.2.1 *Effects of Coactivation on Tactile Acuity.* The fundamental effects of coactivation are illustrated in Figure 2. Shown are two-point discrimination thresholds for 35 subjects plotted versus successive sessions [Godde et al. 1996]. Except for the first session, all subjects show a remarkable stable and reliable baseline of performance with very little scatter. After several hours of coactivation, all subjects without exception improve their acuity as indicated by a lowering of thresholds (pre 1.37 mm $\pm$ 0.21 (mean $\pm$ s.d.), post 1.12 mm $\pm$ 0.22, $n = 35$, $p = .000064$, two-tailed t-test). Retesting after 24 h revealed restoration of initial performance.

These results were the first showing that it is possible to evoke perceptual learning, here the improvement of the sensation of touch in human subjects, solely through a few hours of passive, but temporally patterned stimulation.

To demonstrate the specific, Hebbian nature of the coactivation protocol, that is, the requirement for temporally synchronous stimulation, we compared the effects of coactivation with a so-called single-site

stimulation, where only a small "point-like" skin area was stimulated (cf. Figure 1). Otherwise, stimulation frequency and duration of stimulation period were the same as described for coactivation [Dinse et al. 2003; Godde et al. 1996, 2000; Pleger et al. 2001, 2003; Ragert et al. 2004]. Stimulating for 3 h the tip of the right IF at a single site only led to no changes of thresholds and to no changes in cortical activation, implying that "co"-activation is crucial for the induction of the effects [Pleger et al. 2003].

3.2.2 *Effects of Coactivation on Cortical Maps.* A central question in perceptual learning is how improvement is linked to changes in cortical processing. In order to be able to address this question, we developed a strategy to assess perceptual performance and cortical reorganization in the same subject through a combination of psychophysical tests and noninvasive imaging. Such data sets are a prerequisite to study the correlation between individual changes in behavior and individual changes in brain organization.

To illustrate the cortical effects of coactivation, we used two noninvasive methods to access brain maps. First, we used multisite EEG recordings, the so-called mapping of somatosensory-evoked potentials (SSEP) [Dinse et al. 2003; Pleger et al. 2001]. As a second approach, we used functional magnetic resonance imaging (fMRI) [Pleger et al. 2003]. For SSEP mapping, the source of cortical activity following sensory stimulation is reconstructed by modeling it as a single current dipole. A high goodness of fit of the field produced by the modeled equivalent current dipole to the real measurement provides justification for the procedure. In our case, electric source reconstruction was performed for the so-called N20-component (negativity at 20 ms over primary somatosensory cortex) of the evoked potentials recorded with 32 electrodes after electrical stimulation of the tip of the IF (for an methodological account see Koles [1998]. In the case of fMRI, the BOLD signal (blood-oxygen-level-dependent) is measured, which makes use of the close link between energy metabolism and neural activation. According to recent studies, local field potentials show a high correlation with the hemodynamic response indicating that BOLD signals primarily measure the input and processing of neuronal information [Logothetis et al. 2001]. In both cases, we were interested to map out the location and extent of the index finger representation before and after coactivation. As a general finding, we observed a selective increase in the size of the cortical representation of the coactivated fingers.

Use- and experience-dependent enlargement of cortical maps is a general feature of cortical plasticity and is usually associated with a behavioral or perceptual gain [Dinse and Merzenich 2002; Recanzone 2000]. Our data are in line with animal studies that implied that cortical map size is a reliable predictor of the individual performance. [Recanzone et al. 1992, 1993]. In humans, a correlation between cortical magnification in primary visual cortex (V1) and Vernier acuity has been described, which indicates that Vernier acuity is limited by cortical magnification in V1 [Duncan and Boynton 2003].

Perceptually, the tactile coactivation protocol employed in our study resulted in an overall improvement in all subjects tested, although the amount of improvement was variable throughout the individuals. Similarly, the amount of cortical changes observed varied individually. Under the assumption that changes of cortical maps representing the coactivated index finger reflect changes in cortical processing causally related to the processing of haptic 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 [Dinse et al. 2003; Pleger et al. 2001, 2003]. 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 thresholds, for details about statistical analysis see Pleger et al. [2001, 2003] and Dinse et al. [2003]. Accordingly, small differences in performance must not be due to measurement artifacts or noise, but may reflect true differences in individual brain organization.

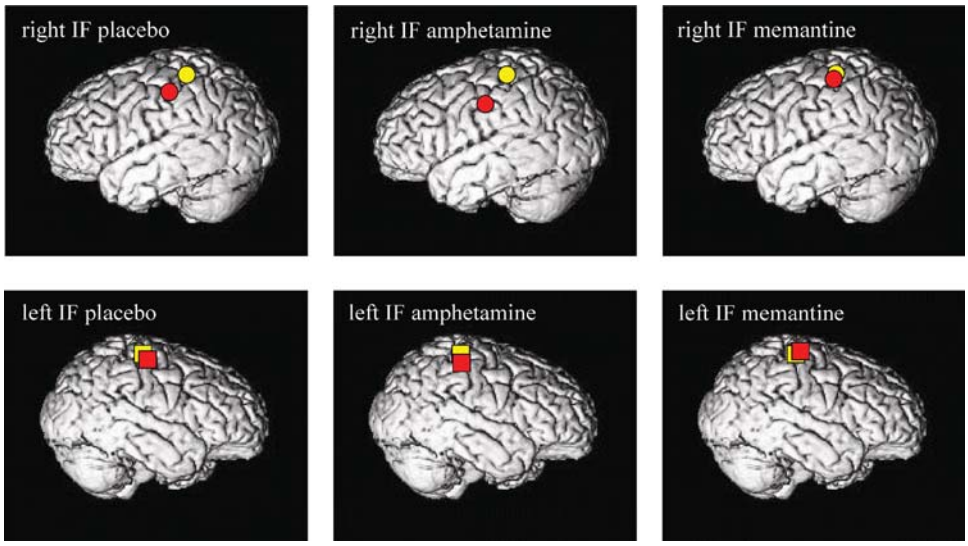

Fig. 3. Schematic projection of the average locations of the single equivalent N20-dipoles of the index finger pre (yellow symbols) and post (red symbols) coactivation onto a 3D reconstructed individual MRI data set. Note the coactivation-induced shift toward the lateral and inferior aspects of the postcentral gyrus in the placebo group, which is nearly doubled in the amphetamine group, but blocked under memantine, a NMDA-receptor blocker. Comparable effects are lacking in the not-coactivated hemisphere (bottom row). Reprinted with permission from *Science* [Dinse et al. 2003].

3.2.3 *Pharmacological Boost of Coactivation-Induced Alterations of Tactile Acuity*. Cellular studies suggest that there might be only a few, basic mechanisms that control synaptic transmission. In particular, the *N*-methyl-*D*-aspartate (NMDA) receptor has been implicated in synaptic plasticity [Cotman et al. 1988; Herron et al. 1986; Lynch 2004]. In order to demonstrate that coactivation is mediated by established plasticity mechanisms, we tested its dependency on NMDA receptor activity. To scrutinize the apparently ubiquitous role of NMDA receptors for unattended learning processes, we used memantine, a substance known to block selectively NMDA receptors [Parsons et al. 1999]. We found that memantine eliminates coactivation-induced learning, both psychophysically and cortically (Figure 3).

While there are many approaches to block plastic processes pharmacologically, less is known about drugs, which enhance cortical plasticity. According to in vitro experiments, alterations of 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 [Scheidtmann et al. 2001; Walker-Batson et al. 2001]. We therefore used amphetamine [Angrist et al. 1987] to test its modulatory role in learning processes evoked by the coactivation protocol.

Application of a single dose of amphetamine (Figure 3) resulted in almost a doubling of the normally observed improvement of tactile acuity (cf. Figure 6) and of cortical reorganization [Dinse et al. 2003]. Combined, our data show that coactivation-induced perceptual learning and associated cortical changes are controlled by basic mechanisms known to mediate and modulate synaptic plasticity. More generally, our data demonstrate that using specific drugs the outcome of coactivation can be further amplified. Given that we are only at the beginning of an understanding of the pharmacology mediating learning, further studies on pharmacological modulators will almost certainly reveal a striking potential of drug applications in order to boost learning and therapy.

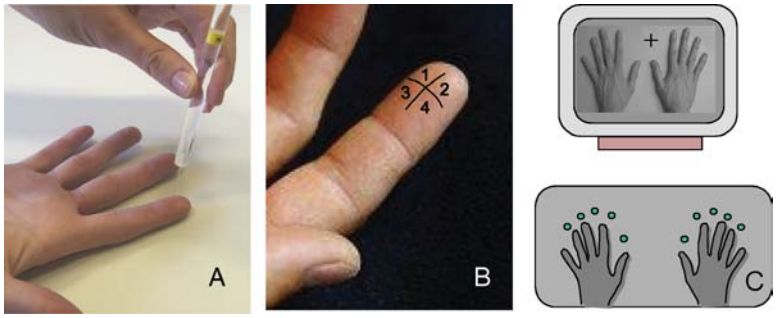

Fig. 4. Illustration of the procedure to assess absolute touch threshold (A) using von Frey hairs, of the localization task (B), where subjects have correctly to identify which of the four quadrants are hit, and of the multiple-choice reaction time (RT) finger selection task (C).

3.3 Remodeling of Haptic Processing and Performance Through Coactivation

Central to coactivation is that it does not require training of a particular tasks, which makes coactivation-induced improvements task independent. Therefore, testing for tactile acuity does not imply that acuity is in some way specific to coactivation. On the contrary, we assume that coactivation alters the entire way of neural processing related to haptic information. Consequently, one can expect that coactivation not only affects two-point discrimination thresholds, but all haptic tasks.

To test this assumption, we initiated a more comprehensive study in which we looked for a number of haptic tasks beyond two-point discrimination. For example, to assess absolute touch thresholds we used von Frey hairs (Marstock, Germany) in a stair case procedure. To investigate localization performance, that is, the ability to localize exactly the absolute skin position that was stimulated, subjects had to indicate without viewing, which of four small quadrants had been touched by a von Frey hair (cf. Figure 4).

As described (Section 3.2.1.), coactivation significantly improves tactile acuity [Dinse et al. 2003; Godde et al. 1996, 2000; Pleger et al. 2001, 2003; Ragert et al. 2004]. In contrast, tactile localization on the IF became impaired by 24% ($p < .0005$) after coactivation, while absolute touch thresholds did not change [Dinse et al. 2005]. The contrasting effects of coactivation on acuity and localization suggest a trade-off between discrimination and localization, and resemble similar findings reported for blind Braille readers [Sterr et al. 1998]. However, closer inspection of the data showed that changes in localization were correlated with changes in discrimination. Subjects that showed only little or no discrimination improvement were those with the largest localization impairment, while subjects that benefited most in discrimination showed only minor impairments, or even also improvements in localization.

A similar balance between different aspects of haptic performance was recently reported for tactile frequency discrimination in the flutter range. While on average coactivation impaired frequency discrimination performance, individual data showed that subjects with little gain in spatial discrimination showed the largest impairment in frequency discrimination, while those with a large gain in spatial acuity showed little changes in frequency discrimination [Hodzic et al. 2004].

In order to explore how coactivation affects more cognitive-demanding tasks, we performed multiple-choice reaction time (RT) measurements in a finger selection task as adopted from Alegria and Bertelson [1970]. An image of each hand was displayed on a monitor and one finger was selected by a visual marker (Figure 4(C)). Subjects had to press the key corresponding to the selected finger on a hand-shaped ten-button keyboard. In addition, dual-choice RTs (left d5 versus right d3, and left d3 versus right d5) were

measured as a control. Our results revealed that RTs were longest for the middle finger (d3) of each hand, but shortest for d1 and d5 of each hand, indicative for a strong end-effect which is typically attributed to classic cognitive paradigms. After coactivation to the right middle finger, the RTs of d3 of the right hand showed a highly significant shorting thereby almost eliminating the end-effect, while RTs of the left hand remained unchanged. When subjects were tested in a dual-choice task, no effects could be observed. Also, no effects were observed in the control group without coactivation [Ragert et al. 2005a].

Analysis of the time course of effects revealed that the effects of end-effect elimination persisted even after 1 week after coactivation. This long-lasting efficacy of coactivation is in contrast to the typical effects observed in a two-point discrimination task, where performance improvement recovered to baseline after 24 h. The long-lasting effects of coactivation observed here provide important evidence that neural processes evoked through unattended activation-based learning protocols can alter haptic performance over a substantial period of time.

According to the data available so far, our initial assumption appears correct, namely that coactivation alters the way haptic inputs are processed. Because there are complex trade-offs between different haptic tasks, it is conceivable that coactivation shifts neural processing into a new regime, where a new balance between tasks is stabilized resulting in newly emerging haptic capabilities.

4. OPTIMIZING AND EXTENDING THE CONCEPT OF ACTIVATION-BASED LEARNING

The most important implication arising from using unattended, activation-based learning protocols comes from the fact that they are passive, that is, they do not require the active participation of the subjects. This might turn out of particularly advantage when such protocols will be used as therapeutic tools in impaired human subpopulations. We therefore attempt to optimize activation-based learning protocols to be able to obtain more control about the magnitude, direction, and stability of the perceptual and behavioral outcome of the resulting learning processes, which is briefly summarized in the following.

4.1 Multifinger Coactivation

As a first step, we recently introduced a modification where all fingers of the dominant right hand were coactivated. For that purpose, the coactivation protocol was applied by means of small devices consisting of solenoids (diameter 8 mm), which were fixed on the tip of each finger of the right hand (d1–d5) to transmit the mechanical pulses to the skin. In this protocol, the aspect of coactivation is twofold: First, receptive fields in the skin portions underneath the solenoids are simultaneously stimulated and thus coactivated. Second, each finger receives stimulation leading to coactivation on all fingertips of the dominant hand [Kalisch et al. 2005]. By means of this protocol, we aimed at activating large portions of the cortical hand representation to induce large-scale perceptual changes. In addition, this design allows to address possible interactions between activated finger representations.

To explore the behavioral consequences of five-finger coactivation, subjects were tested in a number of haptic tasks such as assessment of two-point discrimination thresholds, absolute threshold of touch and localization. To assess haptic object recognition performance, subjects had to identify small cubic objects (Figure 5) solely by haptic impressions without viewing in a recognition task modified according to Newell and coworkers [2001].

We found a massive influence on haptic performance by the five-finger coactivation. Two-point discrimination thresholds were reduced by about 20% on all coactivated fingers, which is a much larger improvement than typically observed for one-finger coactivation (Figure 6). Most remarkably, the number of errors and the time to fulfill the haptic object-classification task were significantly reduced. No effects were found for touch thresholds, in line with pervious findings from one-finger coactivation (see Section 4) [Kalisch et al. 2005]. These results are important as they indicate that adequately designed

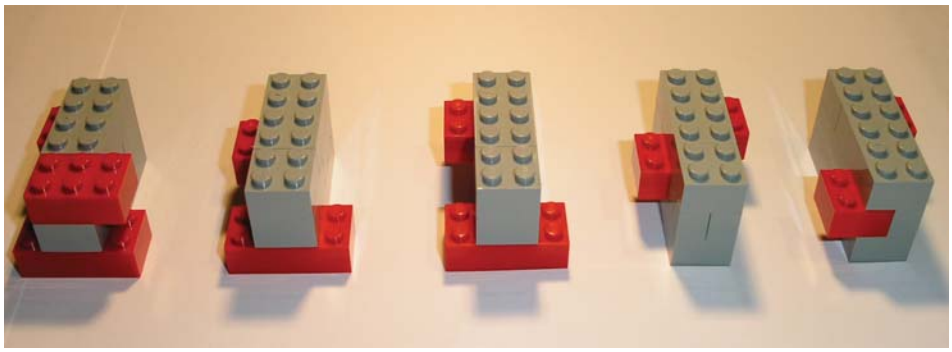

Fig. 5. Examples of objects used in the haptic object discrimination task. Portions of the objects highlighted in red emphasize differences. Subjects were allowed to become familiar with the objects both visually and haptically. In the subsequent recognition, task subjects were asked to identify given objects presented visually by means of haptics only.

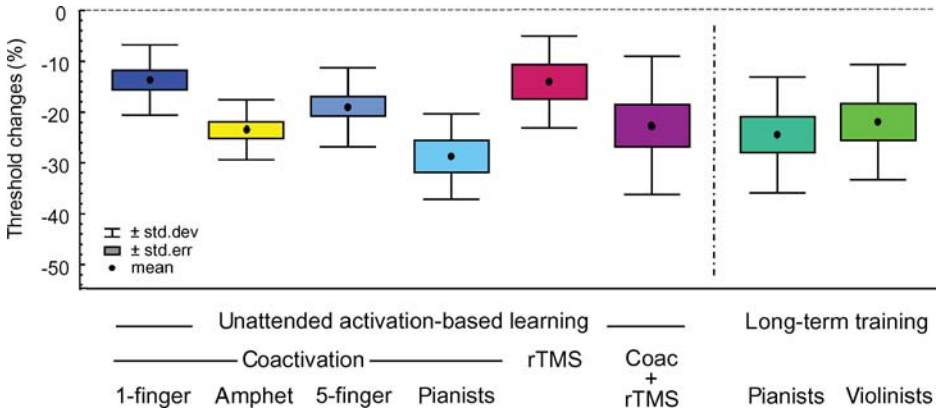

Fig. 6. Comparison of the magnitude of improvement of tactile acuity induced by different forms of unattended activation-based learning protocols and the effects of long-year training in professional pianists and violinists. Shown are percent changes compared to prelearning baseline, or in the case of musicians percent difference compared to a large sample of nonmusician controls. One-finger: standard one-finger coactivation protocol; amphet: boost of one-finger coactivation through amphetamine; five-finger: synchronous coactivation of all five fingers; pianists: one-finger coactivation in pianists; rTMS: 5 Hz rTMS; coac + rTMS: combination of one-finger coactivation with 5 Hz rTMS; pianists and violinists: performance in professional musicians. Data are compiled form Pleger et al. [2001], Dinse et al. [2003], Ragert et al. [2002, 2003, 2004] and Kalisch et al. [2005].

coactivation protocols can evoke not only changes in basic tactile discrimination tasks, but also in much more cognitively demanding haptic object-classification skills.

4.2 Coactivation Using "LTP" Protocols

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 [Bliss and Collingridge 1993; Nicoll and Malenka 1995; Stanton and Sejnowski 1989]. Typically, to induce LTP in brain slices, high-frequency stimulation (HFS, 10 Hz and higher) is used, while LTD can be reliably evoked by low-frequency stimulation (LFS) in the range of 1 Hz. We therefore explored the efficacy of in vitro stimulation protocols to drive also perceptual changes by applying HFS and LFS. HFS consisted of pulse trains that were applied to the tip of the right index finger (IF) with a stimulation frequency of 20 Hz using a small solenoid with a diameter of 8 mm. Each train consisted

of 20 single pulses of 20 Hz lasting 1 s with an intertrain interval of 5 s. LFS was applied at 1 Hz with stimulus trains consisting of 1200 pulses. Duration of HFS and LFS was 20 min each. We found that 20 min of HFS induced a lowering of tactile discrimination thresholds, indicating improved tactile acuity, whereas LFS resulted in an impaired performance on the right, stimulated IF. Most interestingly, 24 h after HFS, we found that spatial two-point discrimination thresholds were still lowered in comparison to baseline. In contrast, 24 h after LFS, discrimination thresholds recovered to baseline conditions [Ragert et al. 2005b].

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 alterations in tactile human discrimination behavior (see also Klein et al. [2004] for perceptual correlates of nociceptive long-term potentiation in humans).

4.3 Role of Timing

Coactivation has the important property that it offers full control about the timing and spacing of stimulation. In all experiments described so far we used the coactivation protocol as described in Section 2.1. (see also Figure 1). In order to take advantage of the aspect of timing control, we developed a modified coactivation device consisting of two tiny stimulators that were independently controlled (diameter of stimulation tips 0.5 mm, separation between tips 5 mm), and that was also taped to the tip of the right index finger. This allowed us to explore the role of correlated inputs for the induction of perceptual learning by comparing correlated (synchronous) with uncorrelated (asynchronous) pairing of tactile stimuli. In detail, for synchronous coactivation an identical Poisson process was used to drive the two stimulators. In case of asynchronous coactivation, two independently generated Poisson processes were used.

After applying synchronous coactivation with two simultaneously controlled stimulators separated by 5 mm that were driven by stimuli derived from a single Poisson process, we also found a lowering of two-point discrimination thresholds on the coactivated IF, confirming the findings described above (Section 3.1.). In contrast, asynchronous coactivation impaired discrimination performance by about the same amount, with no effects on the left, not-coactivated IF. However, when localization was tested, the opposite behavior was found: Synchronous coactivation resulted in an impairment of localization performance, while asynchronous coactivation improved it. Absolute touch thresholds remained unaffected throughout all cases [Dinse et al. 2002, 2005].

The results indicate that manipulating the nature of correlated activity leads to complementary forms of perceptual learning, where different tactile tasks display opposite sensitivities to learning processes. Accordingly, manipulating the type of coactivation stimuli through timing parameters enabled us to switch between discrimination improvement or impairment thus controlling the direction of induced learning.

5. REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS)

Coactivation is not the only form of unattended activation-based learning. Under the assumption that simultaneously applied coactivation induces synchronous neural activity at a cortical site selected by the location of tactile stimulation, we went one step further and shortcut the sensory pathway. To this end, we applied the so-called high-frequency (5 Hz) transcranial magnetic stimulation (TMS) from outside the skull directly to selected brain areas in order to induce synchronous activity.

During a typical rTMS experiment, an electromagnetic coil is placed above the scalp. The coil produces magnetic pulses that pass through the skull and induce electric currents within the brain that alter the activity of the underlying neurons (for review see Grafman and Wassermann [1999], Pascual-Leone et al. [1999, 2000], Siebner and Rothwell [2003]). Repetitive TMS (rTMS) is increasingly used both as a

tool to explore the mechanisms and consequences of cortical plasticity in the human brain and as a new therapeutic strategy. For example, rTMS appears to be effective in improving the mood of people with depression [Kauffmann et al. 2004; Pascual-Leone et al. 1996]. Recently, TMS was shown to expose savant-like skills in normal people by suppressing the left fronto-temporal lobe activity [Snyder et al. 2003].

Using rTMS as a tool to modify directly cortical networks, we could recently demonstrate through a combination of psychophysical assessment of tactile acuity and functional magnetic resonance imaging (fMRI) that two-point discrimination performance of the index finger can be improved parallel to a cortical enlargement of the index finger representation. Applying a total of 2500 TMS pulses to the hand representation in left primary somatosensory cortex in close vicinity of the right IF in two sessions of 9 min each improved tactile acuity by about 15%, a value similar to that found after coactivation (Figure 6) [Ragert et al. 2002; Tegenthoff et al., under revision].

Given that two different forms of unattended activation-based learning, coactivation and rTMS, exert comparable improvements in tactile discrimination performance, we then asked whether enhancement of tactile acuity induced by coactivation can be further improved by a combination of coactivation with 5 Hz rTMS (coac + rTMS). After coac + rTMS, the gain in acuity was 0.35 ± 0.05 (s.e.m.) mm (22.19%), whereas coactivation improvement without rTMS was only 15.73% (repeated measures ANOVA (right IF; pre/post difference coac versus coac + rTMS): $F_{(1,11)} = 6.876$; $p = .024$; factor pre/post $F_{(1.11)} = 37.266$; $p < .0001$). Interestingly, the individual further improvement after coac + rTMS depended on the effectiveness of the coactivation protocol when applied alone. Subjects, who showed little gain in tactile performance after coactivation alone, showed the largest improvement after coac + rTMS implying that the combined application was selective for poor learners [Ragert et al. 2003].

These findings point to an enormous potential of TMS protocols in selectively and purposefully altering brain organization as well as perception and behavior from outside the skull.

6. EFFECTS OF COACTIVATION ON SPECIFIC SUBPOPULATIONS

In the following, we summarize first attempts to alter and improve haptic performance in particular subgroups of human subjects using coactivation.

6.1 Effects of Coactivation on Advanced Subpopulations

Musician's brains constitute an interesting model for neuroplasticity. Imaging studies have demonstrated that sensorimotor cortical representations are altered in musicians [Schlaug 2001; Elbert et al. 1995], which was assumed to arise from the massively altered use of the hands and fingers to accommodate the development of extremely skilled performance. We therefore asked whether cortical reorganization induced by professional musical skill training is paralleled by the evolution of other, unrelated perceptual and learning abilities [Ragert et al. 2004].

Analysis of tactile acuity revealed that long-lasting piano practicing (14 professional pianist) resulted in lower spatial discrimination thresholds in comparison to nonmusicians ($p < .001$ for both hands in comparison to nonmusician controls). In musicians, individual discrimination thresholds were linearly correlated with the daily training duration, indicating a direct link between tactile acuity and the degree of piano practicing (linear correlation analysis (Pearson): right IF: $r = -0.789$, $p = .001$; left IF: $r = -0.799$, $p = .001$). The observed superior spatial discrimination performance in pianists allowed us to address the question, whether the low discrimination thresholds reflect a lower limit in spatial tactile acuity, or whether thresholds are subject to further improvement by learning. Application of the coactivation protocol for 3 h revealed that in pianists acuity could be further improved with the coactivation-induced gain being significantly larger in comparison to control subjects (coactivation-induced gain in

performance of 28% in musicians compared to 12% in nonmusicians; two-sided t-test: $p = .02$) [Ragert et al. 2004].

Our results demonstrate that professional piano players benefit from their daily routine by developing significantly reduced tactile discrimination thresholds, although piano playing is little related to tactile acuity abilities. Most importantly, despite the already high-level MS performance in pianists, coactivation induced a higher gain in discrimination abilities in musicians as compared to controls. This implies stronger capacities for plastic reorganization in pianists, and points to enhanced learning abilities. Interestingly, the coactivation-induced gain in performance correlated with the number of years of extensive piano playing. This kind of metaplasticity suggests that extensive piano practicing alters somatosensory information processing and sensory perception beyond training specific constraints. The data also suggest that the potential of coactivation applies also in subjects characterized by high-level baseline performance.

6.2 Effects of Coactivation on Impaired Subpopulations

We witness a unique restructuring of the aging pattern in the societies of the industrial nations, characterized by an increasing probability to reach high age. Concomitantly, the probability to suffer from age-related disorders is raised dramatically, indicating an urgent need for increasing efforts toward a more comprehensive understanding of the different facets of aging. Aging comprises a number of physiological modifications, including structural and metabolic changes, and getting older is associated with a decline of cognitive and sensorimotor abilities. On the other hand, older adults recruit different brain regions from those recruited by younger adults when performing tasks in the domains of working and episodic memory, which suggest an enormous potential for compensational mechanisms based on a life-long preservation of abilities for reorganization and plasticity [Park 2002; Reuter-Lorenz 2002].

To explore the potential of coactivation in human subpopulations that are characterized by impaired haptic performance, we began to investigate groups of neurologically healthy, but aged subjects.

In humans, tactile acuity is increasingly impaired with increasing age [Stevens and Choo 1995]. To show that the age-related impairment of tactile acuity can be ameliorated by coactivation, we studied discrimination thresholds in healthy subjects aged 66 to 86 years. We found that 3 h of coactivation reduced two-point thresholds in aged subjects similar as described above for young adults. In this way, tactile acuity of an 80-year old subject comes to match that typically found at an age of 50 (ANOVA: $F(2, 72) = 49.971$; $p < .0001$). Our findings demonstrate that the typical age-related decline in tactile performance is not inescapable, but subject to restoration by adequate stimulation procedures [Kleibel et al. 2003]. In interpreting the findings, we assume that the beneficial effects of coactivation result from a combination of plastic-adaptive processes induced by coactivation and of degenerational processes occurring as a consequence of age [Dinse 2005; Godde et al. 2002].

There are reports that density of mechanoreceptors in the skin decreases with increasing age [Bruce 1980; Iwasaki et al. 2003; Vega-Bermudez and Johnson 2004], however, a causal link between impaired acuity and receptor loss remains controversial. On the other hand, neuron number, against popular belief, appears to be stable throughout life [Morrison and Hof 1997], while conduction velocities of peripheral nerves slow down significantly with age [Peters 2002]. It remains therefore to be seen if the performance observed after coactivation represents the lower limit in acuity that can be reached by elderly subjects given the anatomical and morphological constraints arising at high age, or if the discrimination thresholds can be further reduced using more refined stimulation methods. According to new unpublished data from our lab using a five-finger coactivation for 3 h in elderly subjects, discrimination thresholds were lowered by more than 20% for several days, which would favor the second hypothesis.

More generally, the preservation of sufficient tactile acuity into high age is one important prerequisite for the maintenance of independent and autonomous living. We therefore believe that the concept of coactivation might turn out beneficial in preserving everyday sensorimotor competence in the elderly through unattended therapeutical interventions.

7. RELATION OF UNATTENDED ACTIVATION-BASED LEARNING TO OTHER STIMULATION TECHNIQUES

Because attention plays a crucial role in enhancing learning [Buonomano and Merzenich 1998; Dinse and Merzenich 2002; Kilgard 2003], so far limited effort has been made to explore systematically the potential of passive stimulation techniques to evoke brain changes without invoking attention as compared to the development of training measures.

The addition of noise can improve its ability to transfer information reliably, a phenomenon known as stochastic resonance [cf. Bezrukov and Vodyanoy 1997; Collins et al. 1996]. In the case of neural thresholds, small amounts of additive noise can increase the mutual information when inputs are subthreshold. This idea has been applied in humans to improve sensorimotor performance. For example, mechanical noise stimulation was shown to improve vibration and tactile perception in diabetic patients with moderate to severe neuropathy [Khaodhiar et al. 2003]. Application of electrical noise stimulation to the hand of elderly subjects lowered touch thresholds [Dhruv et al. 2002], while noise stimulation to the foot improved sway parameters in young and elderly subjects [Priplata et al. 2003]. These findings suggest that stochastic resonance appears to be effective to interfere with human perception and behavior; however, its relation to coactivation remains unclear. In our view, stochastic resonance affects thresholds by enhancing inputs otherwise subthreshold, while coactivation alters the modes of central processing because of selective changes of synaptic efficacy and synaptic connections. In fact, changing the sign of learning through modification of the type of correlated input (Section 4.3.) would not be possible simply through adding noise.

Another attempt to interfere with human sensorimotor performance is based on electrical stimulation of the whole hand via a wired mesh-glove [Dimitrijevic 1994]. Recently, using fMRI, an increased BOLD response spatially localized within the sensorimotor cortex could be demonstrated after whole hand stimulation below the sensory level for sensation for 30 min [Golaszewski et al. 2004], but so far no studies are available reporting specific changes of haptic performance. It remains to be seen in how far this method compares to coactivation; for possible negative outcomes of this approach see Section 8.

8. LIMITS AND RISKS OF UNATTENDED ACTIVATION-BASED LEARNING

Coactivation as a passive stimulation applied at moderate intensities and frequencies can hardly be expected to exert negative side-effects. Limitations might arise from the short-lasting effects of acuity improvement in the range of 12 to 24 h. However, given that coactivation was applied for only 3 h, the duration of obtained perceptual improvement outweighs the time needed for induction by a factor of almost 5. On the other hand, the five-finger coactivation was shown to evoke stable improvement of acuity for several days, and the protocol of high-frequency coactivation for only 20 min induced acuity improvement that was still present after 24, thereby even further increasing the ratio between induction time to persistence time. Also, the duration of the end-effect elimination for more than 1 week provides evidence that coactivation-induced changes can be long lasting. It should be emphasized that the described effects were obtained after a single session of coactivation. Previous attempts with coactivation applied on three consecutive days indicated that using such a procedure increased stability of changes without affecting magnitude [Godde et al. 2000]. Accordingly, there is evidence that given adequate protocols, coactivation effects can be made rather durable.

As to possible risks, considering the concept behind coactivation, it is conceivable that certain forms of "co-activity" arising in close temporal or spatial vicinity from heavy schedules of stimulation or motor behavior might cause cortical maldaptation [Blake et al. 2002]. For example, repetitive strain injuries such as focal dystonia have a high prevalence in workers who perform intensive, repetitive, sustained, coordinated movements. A recent study in musicians suffering from focal hand dystonia revealed a shrinkage of the hand representations of the affected digits in somatosensory cortex compared to healthy controls [Elbert et al. 1998]. Interestingly, assuming that maldaptation based on coactivation principles contributed to the abnormalities seen in focal dystonia, behavioral therapy using the method of sensory motor retuning leads to substantial restoration of the distorted cortical maps indicating that maladaptation may be reversed by context-specific, intensive training-based remediation [Candia et al. 2003].

The so-called hand-arm vibration syndrome (HAVS) has been associated with prolonged exposure to vibrations transmitted to the human hand-arm system from hand-held power tools and hand-held vibrating workpieces. Patients suffering from HAVS report the development of paraesthesiae or tingling in digits, pain or tenderness in the wrist and hand, digital blanching and cold intolerance in addition to a deteriorated tactile performance such as impairment of frequency and two-point discrimination [Coughlin et al. 2001]. Because vibrations are transmitted by Pacinian receptors that have huge receptive fields covering almost the entire hand, it is conceivably that through mechanisms of "co-activation" the cortical networks undergo maladaptive learning that result in deterioration of haptic processing, which might add and contribute to other factors such as hand-arm mechanics and vascular complications.

More generally, whether the changes resulting from coactivating different skin areas are beneficial or maladaptive may depend on the spatio-temporal characteristics of the stimulation. While five-finger coactivation still improved tactile acuity, coactivation of a larger skin area like the whole hand as is the case during mesh-glove stimulation might impair acuity. However, there is a trade-off between improvement and impairment for different tasks (Section 3.3.). Accordingly, whether a certain form of stimulation is beneficial or not also depends on the defined target task.

9. COMPARING UNATTENDED ACTIVATION-BASED LEARNING WITH LONG-TERM TRAINING

As a rule, acuity improvement after coactivation is in the range of 10 to 20%. Given these numbers, it is not a priori obvious whether such an improvement represents a major advance bearing relevance for everyday life. We therefore asked in how far training-based improvements of sensory skills are comparable in magnitude to those evoked by short periods of activation-based learning. In Figure 6 we have contrasted acuity changes induced by different protocols of unattended activation-based learning applied for minutes to hours with changes found in musicians as a result of long-year training. Surprisingly, acuity changes for pianists [Ragert et al. 2004] and violinists [unpublished data] are almost identical to those obtained after short-periods of unattended activation-based learning, which provides a convincing argument for the functional and behavioral relevance of the latter.

While the duration of acuity changes induced by activation-based learning appears limited (Section 7), little is known about the stability of enhanced performance in musicians. What would be needed is a study about the decay of superior performance after termination of musical skill practicing. However, interpolating from data in normal, nonmusician human subjects whose arms and fingers were immobilized because they had to wear a cast revealed that tactile acuity drops significantly by about 15% within 1 to 2 weeks of immobilization [Ragert et al. 2003]. These data indicate that performance in normal subjects is not stable without maintained practice and use, but that the time constant of this decay is slower than that observed after coactivation.

10. PERSPECTIVES

We have demonstrated the considerable potential of simple, tactile, unattended stimulation protocols that turned out able to modify in a highly selective way a broad range of haptic performance in parallel to major cortical reorganizations.

From a scientific point of view, important lines of research must be devoted to the detailed assessment of the spectrum of coactivation effects on haptic performance. Similarly, efforts must be undertaken to find ways to systematically expand the persistence of the effects in time by making them more durable.

While we have already demonstrated the feasibility of applying this protocol in haptically impaired human populations of high age, further fields of applications have to be defined and tested for feasibility. In parallel, technical devices that optimize coactivation applications must be developed. In this context the efficacy of the five-finger coactivation protocol to affect not only acuity, but also object recognition is of particular interest. Conceivably, such devices might be prime candidates for interfering programs. By the same token, the potential to control the direction of learning through timing adjustments offers substantial perspectives for future therapeutic applications.

The spectacular success of coactivation in aged subjects calls for large-scale usages of coactivation-based principles to maintain and enhance everyday sensorimotor competence. Given the dramatic changes the aging structure in industrialized countries undergoes, and is predicted to undergo in the next decades, such an endeavour becomes more and more vital to modern societies. To make this feasible, stimulation devices must be developed that can be used under rigorous everyday conditions through laypeople at their homes to apply the stimulation protocols that have been tested and developed under laboratory conditions. It is conceivable that by maintaining the sensorimotor competence through devices using the coactivation principle, the ability of elderly people to live largely independent can be significantly prolonged. This not only has major humanitarian implications for the individual, but also for the economy of senior-dominated societies.

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