Proceedings ot the 4th International Conference EuroHaptics 2004

5 - 7 June, 2004
Technische Universität München
München, Germany

Organized by
Institute of Automatic Control Engineering
Technische Universität München
München, Germany
Professor Dr.-Ing./Univ. Tokio Martin Buss

TECHNISCHE
UNIVERSITÄT
MÜNCHEN

Proceedings of EuroHaptics 2004, Munich Germany, June 5-7, 2004.

Improving human haptic sensing in normal and impaired human populations through activation-based learning

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Abstract. Human haptic sensing is not fixed, but subject to major alterations through perceptual learning processes. We describe a new stimulation protocol that allows to improve haptic sensing in humans in a highly systemic way. 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 summarize recent experiments showing that coactivation alters haptic sensing in parallel to major cortical reorganization in somatosensory cortex. We describe first results where coactivation has been utilized for therapeutical purposes in impaired human populations, and we sketch the next steps to be able to apply the concept of coactivation on a regular and reliable basis as a therapeutical tool to selectively interfere with impaired haptic sensing.

1 Introduction

It is common wisdom that perceptual skills improve with training [1]. Consequently, haptic sensing, and thus haptic performance is subject to considerable modification through training, or to enhanced or reduced use [2,3]. Recent studies in "perceptual learning" have revealed 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 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 [4]. 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 [5] or string players [6]. According to these finding, both long-term training and long-term differential use is able to modify haptic sensing.

2 Activation-based learning

We have recently introduced an alternative approach to control and to improve haptic sensing in humans through so-called activation based learning protocols on a very short time scale of only a few hours.

Given the knowledge about brain plasticity accumulated over the last years [7], 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 [8-12]. Coactivation is a task-free, passive stimulation that allows to study systematically the impact of altered input statistics on plastic capacities of cortical networks. The protocol induces perceptual learning in parallel to cortical reorganization without invoking task training, or cognitive factors such as attention or reinforcement [8-12].

Coactivation follows closely the idea of Hebbian learning [13]: 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.

2.1 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) (Fig. 1). The device allows stimulation of the skin portions underneath thereby coactivating the receptive fields within this area. Coactivation-stimuli were drawn from a Poisson process at interstimulus-intervals between 100 to 3000 ms; 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 supra-threshold intensities. Duration of coactivation is 3 hours, see [8-12] for more details.

2.2 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 perceptual learning induced by the coactivation protocol. As a parameter, we mostly used spatial 2-point discrimination thresholds on the tip of the left and right index finger (IF), see chapter 5. for other haptic parameters. Second, the coactivation on the tip of the right IF for a period of 3 hours as a tool to induce perceptual learning. For details of the testing procedure see [8-12]. In brief, to obtain a stable base-line of performance, we tested the subjects on 5 consecutive sessions over several days on the right IF. 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 [8-12]. 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 did not generalize to the IF of the left hand [8-12]. 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.

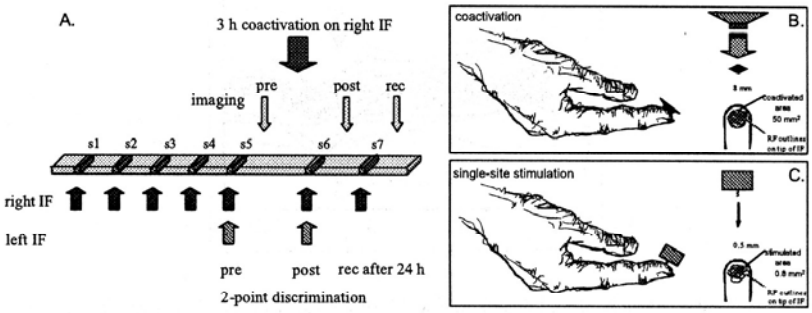

Fig. 1. (*A*) Experimental design: Sessions 1 to 5 (s1-s5) served to create a stable discrimination performance for the right IF. The left IF serving as control is only tested at session s5 (pre coactivation) and after coactivation (session s6, post). After s5, pre-imaging is performed, then coactivation of the right IF is applied for 3 hrs. After the termination of coactivation and after the completion of session 6, post-imaging is repeated. The 7th session (determination of 2-point discrimination thresholds and imaging) was performed to assess the recovery of the coactivation induced effect. (*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 hrs. 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 above for coactivation (see [12] for statistics). Reprinted with permission from Neuron [12]

3 Basic effects of coactivation on tactile acuity and associated cortical maps

The fundamental effects of coactivation are illustrated in Fig. 2. Shown are 2-point discrimination thresholds for 35 subjects plotted versus successive sessions [8]. 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 +/- 0.21 (mean +/- s.d.), post 1.12 mm +/- 0.22, n=35, p=0.000064, 2-tailed t-test). Retesting after 24 hours 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.

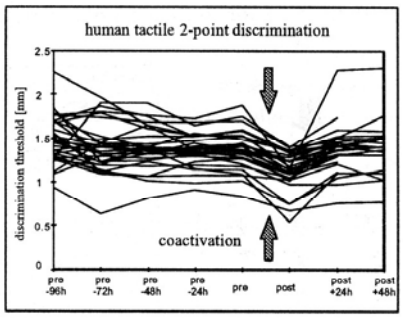

Fig. 2. Tactile two-point discrimination thresholds of the index finger of the right hand as measured in a two-alternative forced-choice discrimination experiment in 35 right-handed human subjects. Thresholds were measured five days before and immediately after coactivation (*arrows*) and on two subsequent days. In all subjects thresholds were reduced immediately after coactivation but returned to control values one day after coactivation. Reprinted with permission from Neuroreport [8]

To demonstrate the specific, Hebbian nature of the coactivation protocol, i.e. 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. Fig. 1). Otherwise, stimulation frequency and duration of stimulation period were the same as described for coactivation [8-12]. Stimulating for 3 hours 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 [12].

3.1 Effects of coactivation on cortical maps

To illustrate the cortical effects of coactivation we used 2 methods that allow non-invasive access to brain maps. First, we used multi-site EEG recordings, so-called mapping of somatosensory evoked potentials (SSEP) [10,11]. As a second approach, we used functional magnetic resonance imaging (fMRI) [12]. 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 of the cortical representation of the coactivated fingers [10-12]. Use- and experience-dependent enlargement of cortical maps is a general feature of cortical plasticity and is usually associated with a behavioural or perceptual gain [2-4].

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. According to animal studies, map size is a reliable predictor of individual performance. 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 [10-12]. 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 statistics see [10-12]. Accordingly, small differences in performance must not be due to measurement artifacts or noise, but may reflect true differences in individual brain organization.

3.2 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. Interestingly, alterations of synaptic efficacy can be modulated by other pharmacological agents thereby acting to gate synaptic plasticity. While there are many approaches to block plastic processes, less is known about drugs, which enhance cortical plasticity. In order to demonstrate that coactivation is mediated by classical plasticity mechanisms, we tested its dependency on NMDA receptor activity. We found that blocking NMDA receptors eliminates coactivation-induced learning, both psychophysically and cortically [11]. We then went one step further and attempted to boost coactivation-induced improvement pharmacologically, here through a single dose of amphetamine [11], which resulted in a doubling of the normally observed improvement of tactile acuity, not only perceptually, but also cortically [11], implying 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 (Fig. 3).

4 Effects of coactivation on impaired subpopulations

Getting older is associated with a decline of cognitive and sensorimotor abilities. In humans, tactile acuity is increasingly impaired with increasing age [14]. 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. Preliminary data revealed that 3 hours of coactivation reduced 2-point thresholds in aged subjects similar as described above for young adults. In this way, tactile acuity of a 80 year old subject comes to match that typically found at an age of 50 (ANOVA: $F(2,72)=49.971$; $p<0.0001$). Our findings show that the typical age-related decline in tactile performance is not inescapable, but subject to restoration by stimulation [15].

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 passive therapeutical interventions.

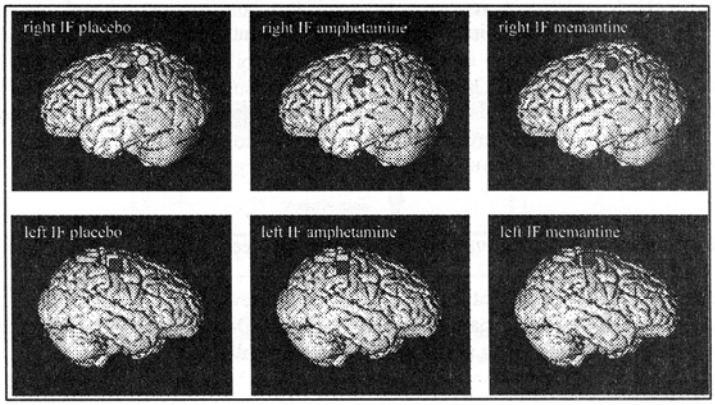

Fig. 3. Schematic projection of the average locations of the single equivalent N20-dipoles of the index finger pre (*light gray symbols*) and post (*dark gray symbols*) coactivation onto a 3D reconstructed individual MRI dataset. Note the coactivation-induced shift towards the lateral and inferior aspects of the postcentral gyrus in the placebo-group, which is nearly doubled in the amphetamine group, but blocked under memantine, a NMDA-receptor blocker. Comparable effects are lacking in the not-coactivated hemisphere (*bottom row*). Reprinted with permission from Science [11]

5 Remodeling of tactile processing and performance through coactivation

A central aspect of coactivation is that it is completely task-free, i.e. coactivation is not related to a particular tactile task. We therefore hypothesized that coactivation will alter the entire way of haptic processing.

To test this assumption, we initiated a more comprehensive study in which we looked for haptic tasks beyond 2-point discrimination. While there is a highly significant improvement in tactile acuity [8-12], we found that tactile localization on the IF became impaired by 24 % ($p<0.0005$) after coactivation [unpublished data]. On the other hand, absolute touch thresholds did not change [unpublished data]. Most intriguingly are preliminary findings indicating that reaction times and even motor tasks benefit from coactivation [unpublished data]. According to these data, 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 con-

ceivable that coactivation shifts neural processing into a new regime, where a new balance between tasks is stabilized resulting in newly emerging haptic including sensorimotor capabilities.

6 Perspectives on passive, unattended activation based learning protocols

Coactivation is not the only form of 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 short-cut the sensory pathway. To this end we applied high-frequency transcranial magnetic stimulation (TMS) from outside the scull directly to selected brain areas in order to induce synchronous activity. Using TMS we could recently demonstrate that 2-point discrimination performance can be improved in a way very similar to coactivation [16] indicating an enormous potential of TMS.

The most important implication arising from using unattended, activation-based learning protocols comes from the fact that they are passive, i.e. 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.

7 Next steps

So far, we have demonstrated the considerable potential of simple, tactile, passive stimulation protocols that turned out able to modify in a highly selective way a broad range of haptic sensations 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.

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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Patents are pending