Tactile Coactivation Resets Age-Related Decline of Human Tactile Discrimination

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Objective: For young subjects, it is well-documented that training and practice improve sensorimotor performance. However, little is known about how the typically observed age-related decline of sensorimotor abilities can be ameliorated by sensory stimulation.

Methods: As an alternative approach to training, we have introduced a tactile coactivation protocol involving Hebbian synaptic plasticity to improve tactile performance on a short timescale of a few hours.

Results: By applying coactivation on the index finger to drive perceptual learning, we demonstrate that in the elderly, aged 65 to 89 years, the age-related impairment of tactile two-point discrimination can be mitigated substantially. In elderly adults, tactile-acuity thresholds increased to 3.5mm compared with 1.5mm found in young adults, whereas 50-year-old subjects showed intermediate performance. As a result of coactivation, discrimination thresholds of the 80-year-old adults came to match those typically found at an age of 50, demonstrating that age-related decline in tactile performance is not irreversible, but rather subject to considerable restoration by specific stimulation protocols.

Interpretation: Because the preservation of sufficient tactile acuity into advanced age is an important prerequisite for the maintenance of autonomous living, we believe that the concept of coactivation might turn out to be beneficial in preserving everyday sensorimotor competence in the elderly through new forms of therapeutic interventions.

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In humans, tactile acuity is progressively impaired with increasing age.[1–3] This perceptual decline is regarded as a typical signature of the overall physiological, structural, and metabolic changes that occur during aging contributing to the age-related impairment of sensorimotor and cognitive abilities. In contrast, it is well acknowledged that extensive training and repeated practice improves perceptual and motor skills, a phenomenon based on neuroplasticity principles.[4–7] As an alternative approach to training, we recently have introduced tactile coactivation to control and to improve tactile performance in humans on a short timescale of only a few hours.[8–13] Coactivation comprises passive, unattended synchronous stimulation of a patch of skin and produces focal activation of the corresponding neural representations.[13] A major advantage of coactivation is that it is applied passively, and thus does not require active cooperation of the subjects. To interfere with the aging-related impairment of tactile perception, we used tactile coactivation as an intervention to demonstrate that the age-related decline in sensory performance typically observed in elderly human subjects[1–3] is subject to plastic reorganizational processes, and therefore can be ameliorated through brief periods of this specific form of tactile stimulation.

Subjects and Methods

Participants and Age Groups

For details of design and schedule see Figure 1A and Goode and colleagues',[8] Pleger and colleagues',[9,10] Dinse and colleagues',[11,13] and Ragert and colleagues'[12] articles. We tested 120 subjects; all subjects were right-handed according to the Edinburgh Handedness Inventory. As control subjects, we tested 79 young subjects aged 20 to 30 years (mean, 24.4 ± 3.05 years). In addition, 13 subjects aged 47 to 55 years (mean, 51.2 ± 2.61 years) were studied. The target group consisted of 28 subjects aged between 66 and 86 years (mean, 74.9 ± 5.4 years; 15 women). Older adults were recruited by poster announcements in senior residences. All subjects underwent neurological examination and were without neurological symptoms and were in good physical condition. Eligibility criteria were lucidity, independence in activities of daily living, and absence of motor and sensory handicaps and of any impairment due to arthritis or other causes of joint immobility. Subjects with visual or hearing loss, with past or present diseases of the central or peripheral nervous system, or taking central nervous system–acting

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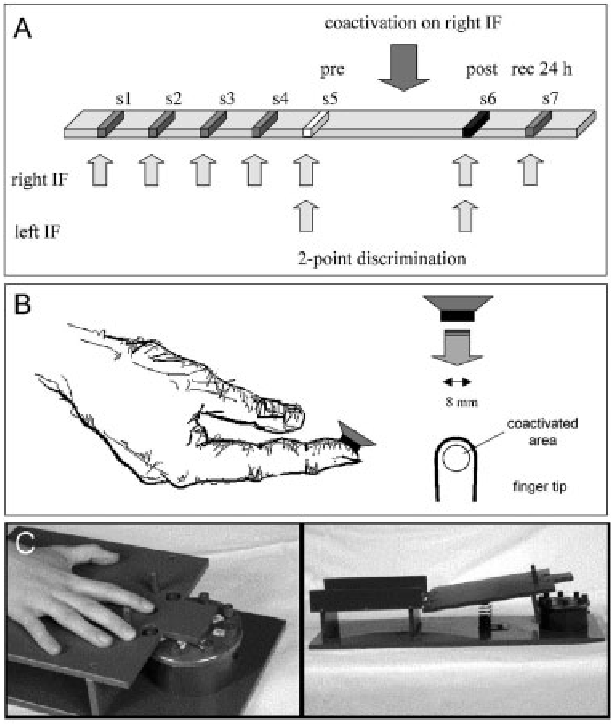

Fig 1. (A) Experimental design. Sessions 1 to 5 (s1–s5) served to create a stable discrimination performance for the right index finger (IF). The left IF serving as control for transfer of learning was tested only at s5 (before coactivation, pre) and after coactivation (s6, post). After s5, coactivation of the right IF was applied for 3 hours. After termination of coactivation, thresholds of each hand were retested. The seventh session was performed to assess the recovery of the coactivation-induced effect after 24 hours. (B) Application of coactivation. A small solenoid with a diameter of 8mm was mounted on the tip of the right IF to coactivate the receptive fields representing the skin portion under the solenoid (the coactivated skin area of the tip of the IF is indicated). (C) Device to measure spatial two-point discrimination thresholds. To accomplish uniform stimulation, we installed the disc containing the needles in front of a plate that could be moved up and down. The arm and fingers of the subjects were fixed on the plate and the subjects were then asked to move the arm down. The test finger was held in a hollow containing a small hole through which the finger touched the needles with approximately the same indentations in each trial.

medication were excluded. Cognitive abilities were assessed using the Mini-Mental State Examination. Only subjects scoring 27 to 30 of 30, indicative of "no dementia," participated in the study. The study was performed in accordance with the Declaration of Helsinki. The subjects gave their written informed consent, and the protocol was approved by the local ethical committee of Ruhr-University Bochum.

Experimental Schedule

The experiments consisted of two different components: (1) the measurement of two-point discrimination thresholds on the tip of the left and right index fingers (IFs) as an indicator for perceptual performance and as an indirect marker of cortical reorganization; and (2) 3-hour coactivation on the right IF to induce perceptual improvement of discrimination performance (see Fig 1A). To obtain a stable baseline of discrimination, we tested the subjects on five consecutive sessions on the right IF. Sessions were analyzed statistically for stability (analysis of variance [ANOVA]). In the fifth session, measurements of the thresholds of the left IF were additionally performed. Previous studies had shown that the coactivation effect on the right IF did not transfer to the IF of the left hand.[8–13] We therefore used the IF of the left hand as a control and for the assessment of possible nonspecific side effects of coactivation. After the assessment of discrimination performance on both the test and the control finger (precondition), coactivation was applied to the right IF (see Fig 1B). Discrimination performance on the IF of each hand was retested starting about 30 minutes after the termination of the coactivation protocol (postcondition). Recovery of coactivation-induced changes was assessed 24 hours after coactivation in the seventh session.

Coactivation

To apply coactivation in elderly subjects, we used the same procedure as described in our previous studies[8–13]: A small device consisting of a solenoid with a diameter of 8mm was taped to the tip of the right IF (compare with Fig 1B). The device allowed stimulation of the skin portions underneath, thereby coactivating the mechanoreceptors within this area. Coactivation stimuli were drawn from a Poisson process at interstimulus intervals between 100 and 3,000 milliseconds; average stimulation frequency was 1Hz, and the duration of each pulse was 10 milliseconds. To demonstrate the Hebbian nature of coactivation, we recently have shown that stimulating a small skin area caused neither changes of thresholds nor changes in cortical activation, implying that *co*activation is indeed crucial.[10] The pulse trains required to drive the solenoid were recorded on tape and were played back via portable tape recorders, permitting unrestrained mobility of the subjects during coactivation. Subjects were instructed not to attend to the stimulation. In fact, all subjects resumed their normal day's work. Coactivation stimuli were applied at suprathreshold intensities. Laser vibrometer measurements showed that the actual amplitude was 10 to 20μm. Duration of coactivation was 3 hours.

Measurement of Two-Point Discrimination Thresholds

Tactile spatial two-point discrimination thresholds of the tip of the IFs were assessed using the method of constant stimuli as described previously.[8–14] To overcome problems in the use of two-point measurements associated with handheld probes,[15,16] we used a specifically designed apparatus that allows a standardized and objective form of testing (see Fig 1). To extract thresholds, we obtained psychometric curves based on many repeated stimulus presentations. Test–retest reliability was 0.90 for the young subjects, 0.97 for the intermediate-age group, and 0.88 for the elderly. According to our own unpublished data, acuity thresholds obtained by gratings[15,16] or by two-point measurements were highly equivalent (Pearson's correlation, $r = 0.7160$, $p < 0.0005$, N = 22 subjects), although thresholds obtained by gratings are slightly lower in general. Seven pairs of needles (diameter, 200μm) were used (see Fig 1C). In addition, zero distance was tested with a single needle. The subjects had been instructed that single needles would be presented occasionally for control purposes, but they did not know how often. The number of single-needle presentations was 1 in 8, ie, 10 presentations in 1 session. For most subjects, false alarm rates were zero. Closer inspection of the data showed that false alarms were zero under each condition in the young group, 0.4 ± 0.35 and 0.9 ± 0.89 (average percentage errors ± standard error of the mean) for the right and left IFs of the intermediate-age group, 0.4 ± 0.31 and 0.4 ± 0.44 for the right and left IFs of the elderly, and 0.4 ± 0.44 for both fingers of the elderly after coactivation. To account for the age-related decline in acuity, we used different needle distances for the different age groups: 0.7, 1.0, 1.3, 1.6, 1.9, 2.2, and 2.5mm for the young group; 1.0, 1.4, 1.8, 2.2, 2.6, 3.2, and 4mm for the middle-aged group; and 1.5, 2.3, 3.1, 3.9, 4.7, 5.6, and 7.0mm for the older group. The needles were mounted on a rotatable disc that allowed us to switch rapidly between distances (see Fig 1C). Each distance of the needles was tested 10 times in randomized order resulting in 80 single trials per session. Subjects had to decide immediately whether they 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 (SPSS; SPSS, Chicago, IL). Threshold was taken from the fit at the distance where 50% correct responses was reached.

Results

We assessed tactile 2-point discrimination performance of the IFs in 28 older right-handed neurologically healthy subjects aged 66 to 86 years (mean, 74.9 ± 5.4 years; 15 women). To obtain a stable baseline of discrimination, we tested the subjects' performance with the right IF in five consecutive sessions over several days (Fig 2A for elderly subjects). All subjects achieved a stable performance as estimated from repeated assessment of thresholds over five consecutive sessions. Average threshold of the older group was 3.42 ± 0.50mm (mean ± standard deviation). In contrast, mean threshold of a young control group was 1.58 ± 0.17mm (79 subjects; age range, 20–30 years; mean age, 24 ± 3.0 years). In addition, we tested 13 subjects aged 47 to 55 years. Threshold in this intermediate-age group was 2.61 ± 0.48mm, indicating that an age-related decline is present already at that age, although minor in extent. According to univariate ANOVA (with factor AGE $F_{(2,118)} = 347.785$; $p < 0.001$), the differences across the three age groups were significant. Post hoc analysis (Bonferroni corrected for multiple comparison) showed: young vs old, $p < 0.001$; young vs middle age, $p < 0.001$; middle age vs old, $p < 0.001$). For individual psychometric curves, see Figure 2 for a young (see Fig 2B) and an elderly subject (see Fig 2C). All single-subject discrimination thresholds are plotted in Figure 3 as a function of age (linear Pearson's correlation, $r = 0.899$, $p < 0.0001$). Whereas in elderly, the thresholds of the left IF were, on average, lower by 0.38mm (two-sided paired t test left vs right: $p = 0.026$); in young subjects or subjects of the intermediate-age group, no differences between thresholds of both hands were found.

We then asked whether the documented aged-related decline in acuity is irreversible, or whether the decline can be ameliorated by learning processes evoked by tactile stimulation. To this end, we applied coactivation in all older subjects (n = 28; age rage, 66–86 years) using the same coactivation protocol as applied in previous studies.[8–13] In the older subjects, coactivation lowered thresholds to 2.89 ± 0.40mm after coactivation (see Fig 2A). Previous studies had shown that the coactivation effect to the right IF did not transfer to the IF of the left hand.[8–13] We therefore used the IF of the left hand as a control and for the assessment of possible unspecific side effects of coactivation. No effects were seen on the left IF, suggesting localization of the effect with no transfer to the other hand (repeated-measures ANOVA with SESSION as repeated measure: right IF (precondition, postcondition, and recovery): $F(2,72) = 49.971$; $p < 0.0001$, Bonferroni-corrected paired comparison (precondition vs postcondition): $p < 0.0001$; left IF (precondition, postcondition): $F(1,29) = 2.383$; $p = 0.133$. Assessment of reversibility showed that thresholds of the right IF recovered to baseline conditions 24 hours after coactivation (3.33 ± 0.46mm; Bonferroni-corrected paired comparison (precondition vs recovery): $p > 0.05$, not significant); see Figure 2A for group effects and Figure 2C for single-subject data. Both the lack of transfer and the time course of reversibility are findings also typically observed in young subjects.[8–13] For comparison, all young subjects were also submitted to the coactivation protocol. We found a lowering of thresholds in the young group from (mean ± standard deviation) 1.55 ± 0.19mm to 1.33 ± 0.19mm (repeated-measures ANOVA with factor precondition vs postcondition: $F_{(1,78)} = 268.964$; $p < 0.0001$). In Figure 3, discrimination thresholds after coactivation of the young and the elderly are highlighted (pink symbols). In young subjects, the gain in discrimination threshold was (mean ± standard deviation) 0.22 ± 0.19mm, but in elderly subjects, the mean improvement was 0.54 ± 0.32mm (univariate ANOVA with AGE: $F_{(1,105)} = 56.787$; $p < 0.001$; Fig 4A). These results demonstrate that the tactile coactivation protocol is also effective at high age, improving discrimination thresholds in subjects up to 89 years old. Comparing thresholds found in the intermediate-age group with those obtained in the elderly before coactivation showed a clear difference, which, however, disappeared after coactivation (univariate ANOVA precondition: $F_{(1,40))} = 23.979$, $p < 0.0001$; postcondition $F_{(1,40)} = 3.527$, $p > 0.05$). To show statistically the equality of means, we approached this problem by empirically sorting the data into two groups via cluster analysis and compared the empirical group assignment thus achieved with the age group assignment. The assignments were not significantly correlated (Kendall's τ or Spearman's ρ, $r = 0.278$, $p > 0.05$), which provides strong evidence that the thresholds of elderly subjects after coactivation may not be separated from those of the 50-year-old group based on empirical criteria. In contrast, in the precondition, the data of elderly subjects can be separated from those of the intermediate-age group (Kendall's τ or Spearman's ρ, $r = 0.51$, $p = 0.001$). As a result, the tactile acuity of the elderly subjects after coactivation came to match the average performance of subjects aged 47 to 59 years.

Discussion

Our data demonstrate that synaptic plasticity induced by coactivation improves tactile acuity in discrimination-impaired elderly. However, even after coactivation, the lowest thresholds in elderly (2.34mm) were still above thresholds typically observed in young subjects (approximately 1.5mm, see Fig 3).[8–13] Linear correlation analysis (Pearson's) showed that the magnitude of coactivation-induced changes in the elderly group were dependent on the performance level under preconditions in a systematic manner (see Fig 4B): Subjects with the highest prethresholds showed the largest improvement, whereas subjects with low prethresholds showed only limited improvement, which points toward the presence of ceiling effects. Further experiments are therefore required to clarify whether the performance observed after coactivation represents the lowest limit in acuity that can be reached by elderly given the anatomical and morphological changes accumulating over age, or whether discrimination thresholds can be further reduced using more refined intervention methods.

As to possible left- and right-hand differences of tactile perception, Meador and coworkers[17] had applied brief electric pulses to the IF of one or both hands, which showed that perceptual thresholds in healthy subjects were lower in the left than the right hand. Our

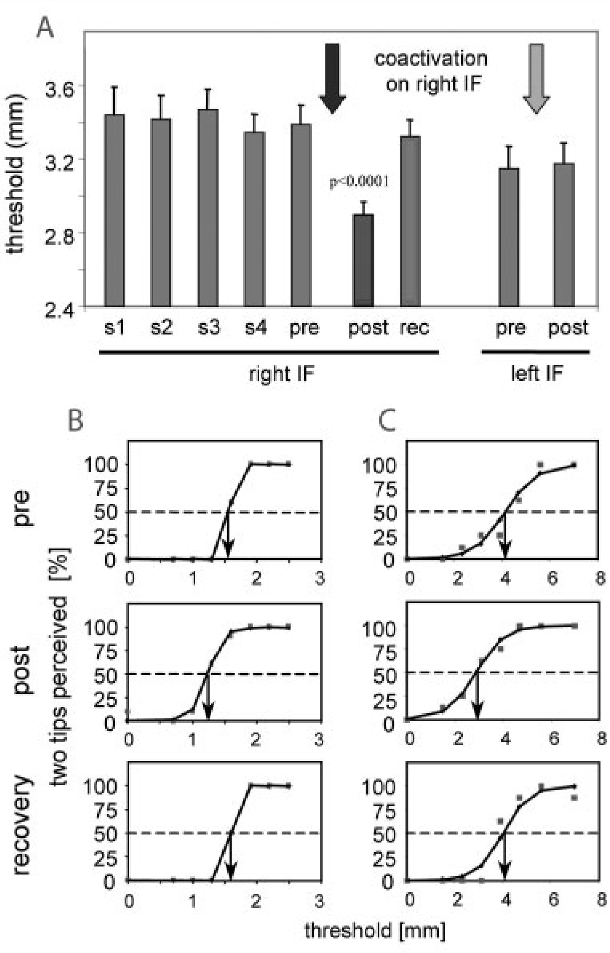

Fig 2. (A) Effects of coactivation on discrimination thresholds. Average data (standard error) from all elderly subjects (n = 28). Coactivation period (3 hours) of the right index finger (IF) is indicated by arrows *(for details of the experimental design and the stimulation protocol see Fig 1A). Shown are results from five consecutive sessions (s1–s5, s5 = pre) before coactivation of the right IF. After s5 (precondition), coactivation was applied* (black arrow). *After coactivation, discrimination thresholds were significantly reduced. Twenty-four hours after coactivation, we found two-point discrimination thresholds on the right IF similar to those obtained before coactivation. Discrimination thresholds obtained for the control finger (left IF) after coactivation of the right IF (IF of the left hand was not coactivated;* grey arrow*) for the precondition and postcondition showed that there is no transfer of the coactivation effect to the contralateral finger. (B, C) Psychometric functions illustrating the discrimination performance obtained before (pre), after (post), and 24 hours after coactivation for a young (B) and an elderly subject (C). Correct responses in percentages* (squares) *are plotted as a function of separation distance together with the results of a logistic regression line* (diamonds). *A 50% level of correct responses is indicated* (dashed line) *together with resulting thresholds* (arrows). *(Top) Precondition before coactivation; (middle) postcondition, immediately after coactivation; (bottom) recovery condition, 24 hours after termination of coactivation. In both the young (26 years old) and the elderly subject (81 years old), after coactivation there is a distinct shift in the psychometric functions toward lower separation distances, which recover to preconditions 24 hours later. In the young subject, thresholds were reduced from 1.56 to 1.23mm after coactivation, and recovered back to baseline (1.59mm). In the elderly subject, thresholds were reduced from 4.2 to 2.8mm, thereby matching prethresholds typically found in 50-year-old subjects (mean threshold of 13 subjects aged 47 to 55 years was 2.61 ± 0.48mm). Twenty-four hours later, threshold recovered back to baseline (4.1 mm).*

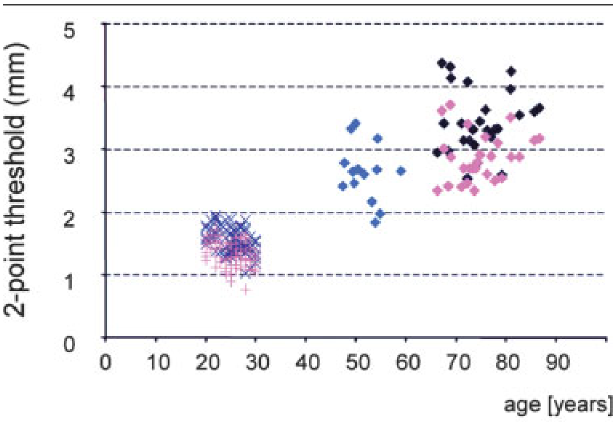

Fig 3. Tactile two-point discrimination thresholds of the tip of the right index finger as a function of age (total of 120 subjects). After coactivation (violet symbols), *thresholds of the coactivated subjects (young control group and elderly group) were significantly reduced. Coactivation-induced improvement in the group aged 66 to 86 years was several-fold 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 to 55 years.*

own observations using von Frey hairs to measure touch thresholds are consistent with such findings.[18] In contrast, about spatial acuity, no differences between the homologous fingers of the two hands have been reported.[19,20] We can confirm this observation, as even in a large sample of young subjects we never observed differences between the same fingers of both hands for two-point thresholds. Accordingly, that tactile acuity differs between hands in elderly subjects can be taken as an indication that thresholds of the left hand are less susceptible to age-related impairment than those of the right hand.

To obtain information about cortical sites involved in mediating the observed synaptic plasticity, we have previously combined the assessment of discrimination thresholds with recording of somatosensory-evoked potentials or with functional magnetic resonance imaging before and after coactivation in young human subjects. These data showed that the coactivation-induced gain of perceptual performance was correlated linearly with the amount of cortical reorganization of the finger representation in primary somatosensory cortex.[9–11] It is therefore conceivable that in the elderly, synaptic plasticity localized in somatosensory cortex are likely to be involved in mediating the amelioration of age-related impairment of tactile acuity. For a discussion about the relation of coactivation-induced changes of synaptic plasticity and learning processes see Dinse and colleagues’[13] and Tegenthoff and colleagues’[14] articles.

Coactivation closely follows the idea of Hebbian learning: Synchronous neural activity, which is regarded instrumental to drive plastic changes, is generated by the simultaneous tactile “costimulation.” To demonstrate the Hebbian nature of coactivation, we recently demonstrated that stimulating a very small skin area caused neither changes of thresholds nor changes in cortical activation, implying that *co*activation is indeed crucial.[10]

Improvement of acuity after coactivation is typically between 15 and 20%. Given these values, it is not a priori clear whether such an improvement represents a major advantage bearing relevance for everyday life. We therefore compared training-induced improvements of tactile acuity described for pianists[12] and violinists (unpublished data) with those evoked by coactivation. Surprisingly, discrimination gain is almost identical for long-term training and short-time coactivation.[13]

As described, the effects in young and elderly recov-

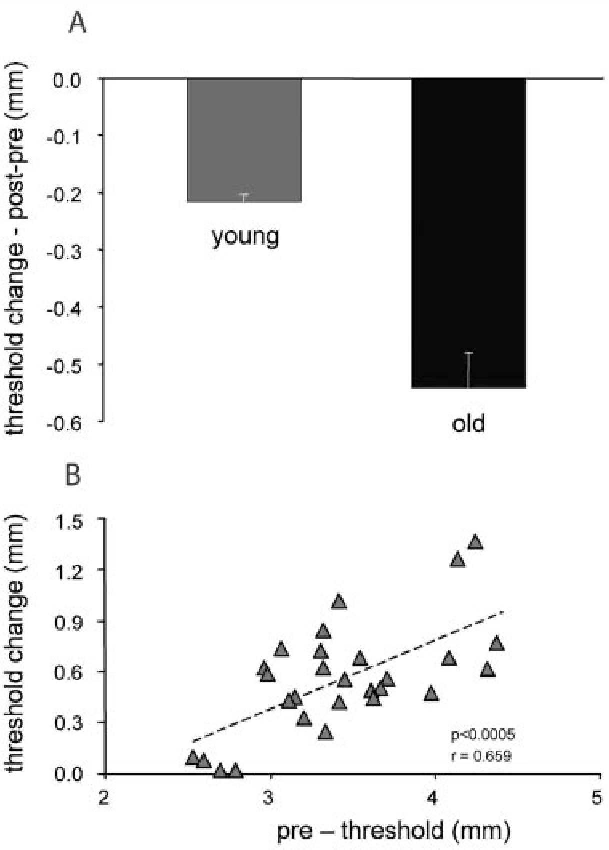

Fig 4. (A) Comparison of the amount of coactivation-induced lowering of discrimination thresholds between young and elderly. Shown are average precoactivation − postactivation differences in threshold and standard error. (B) Linear correlation analysis (Pearson’s) between thresholds on the right index finger under preconditions and the magnitude of discrimination threshold changes (postcoactivation − precoactivation). We found a significant correlation ($r = 0.659$; $p < 0.0005$) *indicating that prethresholds determine the amount of coactivation-induced improvement.*

ered to baseline within 24 hours (Session 7). In a previous study in young subjects, the time course of recovery was more closely analyzed; it was found that significant improvements were observed up to 6 hours after coactivation.[8] Accordingly, it is desirable to increase the durability of the effects. Applying coactivation on 3 consecutive days had no effect on the magnitude of changes, but the effects were maintained throughout the next 24 hours. Only on day 5 did the thresholds return to preconditions.[8] Coactivating all fingertips of a hand instead of a single finger resulted in much stronger and longer lasting effects.[18] Another alternative is the use of high-frequency tactile stimuli mimicking long-term potentiation–like stimulation. Application of high-frequency tactile coactivation for only 20 minutes evoked tactile acuity improvements comparable in magnitude, which recovered to baseline only after 48 hours.[21] Conceivably, combining repeated applications with new forms of coactivation protocols will lead to higher persistence of the evoked improvement.

The typical approach to ameliorate age-related changes is to subject elderly to intense schedules of training and practicing, and there is no doubt about the effectiveness of training-based intervention even at an advanced age.[22–25] However, because many elderly individuals suffer from restricted mobility, additional and alternative approaches are needed that supplement and enhance, or even replace, conventional training procedures. Following this rationale, promising results recently have been reported in cases where action observation was used to enhance the effects of motor training on memory encoding in older adults[26]; see also Hummel and Cohen’s[27] and Sawaki and colleagues’[028] articles for a related approach in the field of stroke rehabilitation.

The unique advantage of coactivation is its passive nature; ie, it does not require the active cooperation and involvement of the subject, but can be applied even in parallel to other occupations and might therefore be substantially easier to implement. These properties, together with the effectiveness of coactivation to improve tactile perception even in elderly individuals, make coactivation-based principles prime candidates for therapeutic intervention programs that serve as a training substitute in impaired populations.

There have been alternative attempts to interfere with the age-related decline of sensory capacities. For example, the addition of noise can improve the ability to reliably transfer information, a phenomenon known as stochastic resonance. Electrical noise stimulation to the hand of elderly subjects lowered touch thresholds,[29] whereas noise stimulation to the foot improved sway parameters in young and elderly subjects.[30] Whereas stochastic resonance affects thresholds by enhancing inputs that would otherwise be subthreshold, coactivation most likely alters the modes of neural processing due to specific changes of synaptic efficacy and synaptic connections.[9–11] Taking a pharmacological approach, a recent report showed enhanced encoding of motor memories in elderly adults, up to levels present in younger subjects, by restoring dopaminergic function in the elderly subjects through administration of a single oral dose of L-dopa.[31] Accordingly, there is agreement that age-related decline of perception and behavior can at least be ameliorated.

Anatomical and morphological changes that affect the hand and fingers and develop with age are numerous. For example, the density of mechanoreceptors in the skin decreases with increasing age,[32] and conduction velocities of peripheral nerves slow down significantly with age.[33] Yet, a causal link between impaired acuity and receptor loss remains controversial.[34] At a neural level, cognitive impairments during nonpathological aging have been suggested to reflect synaptic alterations in otherwise intact circuits rather than neuron loss, an important prerequisite for possible reversibility.[35,36] Accordingly, despite the accumulation of degenerative processes during aging, our findings demonstrate that the typical age-related decline in tactile performance is not inevitable, but rather subject to restoration by stimulation procedures that rely on Hebbian learning principles. We therefore assume that despite the development of degenerative processes, capacities for plasticity and learning are maintained even at advanced age. As a result, the beneficial effects obtained after coactivation may represent the outcome of new cortical-processing strategies that develop as a consequence of both plastic-adaptive processes induced by coactivation and degenerational processes developing over age.[37,38]

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

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