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Functional Imaging of Perceptual Learning in Human Primary and Secondary Somatosensory Cortex

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Summary

Cellular mechanisms underlying synaptic plasticity are in line with the Hebbian concept. In contrast, data linking Hebbian learning to altered perception are rare. Combining functional magnetic resonance imaging with psychophysical tests, we studied cortical reorganization in primary and secondary somatosensory cortex (SI and SII) and the resulting changes of tactile perception before and after tactile coactivation, a simple type of Hebbian learning. Coactivation on the right index finger (IF) for 3 hr lowered its spatial discrimination threshold. In parallel, blood-oxygen level-dependent (BOLD) signals from the right IF representation in SI and SII enlarged. The individual threshold reduction was linearly correlated with the enlargement in SI, implying a close relation between altered discrimination and cortical reorganization. Controls consisting of a single-site stimulation did not affect thresholds and cortical maps. Accordingly, changes within distributed cortical networks based on Hebbian mechanisms alter the individual percept.

Introduction

Extensive use or training is paralleled by substantial changes in cortical representations, thereby emphasizing the relevance of cortical plasticity for everyday life (Braun et al., 2001; Buonomano and Merzenich, 1998; Dinse and Merzenich, 2002; Elbert et al., 1995; Pascual-Leone and Torres, 1993; Recanzone et al., 1992; Recanzone, 2000). To study a particular form of perceptual learning in parallel to cortical reorganization, we recently introduced a coactivation protocol that closely followed the idea of Hebbian learning: synchronous neural activity, necessary to drive plastic changes, is evoked by tactile coactivation of the skin (Godde et al., 1996, 2000; Pleger et al., 2001). From a number of animal studies, the importance of temporally correlated inputs has been assumed to play a key role in mediating plastic changes (Clark et al., 1988; Fregnac et al., 1988). In fact, since Hebb (1949), and even since James (1890), the aspect of simultaneity has become a metaphor in neural plasticity. In the coactivation protocol, reorganization is driven passively by manipulating the characteristics of the input statistics without invoking training of a task or cognitive factors such as attention or reinforcement.

In previous studies, we have demonstrated that a few hours of coactivation of skin surfaces on the hindpaw of adult rats resulted in reversible reorganization of somatosensory cortex (Godde et al., 1996): cortical maps enlarged, thereby creating a joint representation of the coactivated skin sites. To show that plastic changes induced by coactivation bear relevance at the perceptual level, we assessed spatial tactile discrimination performance as a marker of plastic reorganization in human subjects. In these experiments, discrimination thresholds were measured before and after coactivation of a small skin region on the tip of the index finger. After 3 hr of coactivation, we found a lowering of thresholds, an effect that was reversible within 24 hr (Godde et al., 2000). Combining measurements of somatosensory evoked potentials (SSEP) in primary somatosensory cortex (SI) and of tactile discrimination thresholds showed a close correlation between the amount of coactivation-induced perceptual improvement and the degree of individual cortical reorganization (Pleger et al., 2001; Dinse et al., 2003).

Most of our knowledge of plastic reorganization comes from studies in primary somatosensory cortex (SI). We therefore extended our approach of correlating psychophysical performance with cortical reorganization to the investigation of plastic changes in secondary somatosensory cortex (SII). While in animal models maps can be derived in great detail, evidence in humans is mostly indirect, resulting from calculating the positions of current sources obtained from electrical or neuromagnetic evoked potentials. We therefore used functional magnetic resonance imaging (fMRI) to assess the position and the size of cortical finger representations in SI and SII before and after tactile coactivation in order to demonstrate a link between cortical map changes and altered perception.

Results

Effects of Coactivation on Discrimination Thresholds

We tested 14 right-handed subjects (4 male, 10 female; mean age 31.6 years, SD $\pm$ 3.7 years) in a 2-alternative forced-choice simultaneous spatial 2-point discrimination task (Godde et al., 1996, 2000; Pleger et al., 2001; P. Ragert et al., 2001, Soc. Neurosci., abstract; Dinse et al., 2003); for experimental setup and design, see Figure 1. Prior to coactivation, all subjects achieved a stable 2-point discrimination performance as estimated

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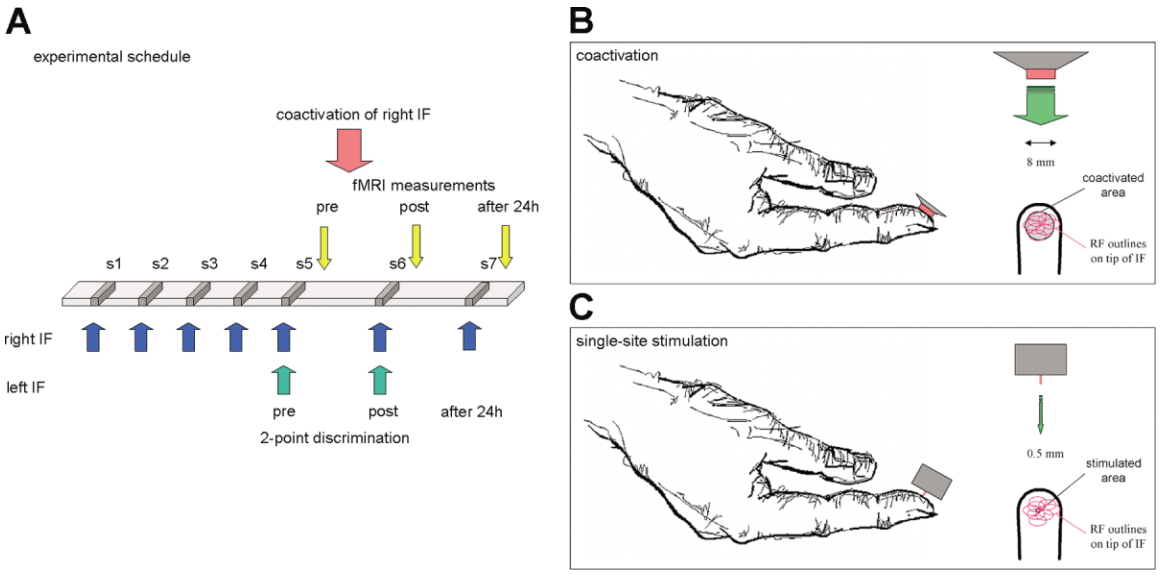

Figure 1. Coactivation Schedule and Procedure

(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 (precoactivation) and after coactivation (session S6, post). After S5, pre-fMRI measurements are performed, and then coactivation of the right IF is applied for 3 hr. After the termination of coactivation and after the completion of session 6, post-fMRI measurements are repeated. The seventh session (determination of 2-point discrimination thresholds and fMRI measurement) 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 hr. The experimental 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.

from repeated assessment of thresholds over five consecutive sessions (Figure 2A). After coactivation, discrimination thresholds were reduced from 1.58 ± 0.20 mm (mean ± SD) to 1.28 ± 0.25 mm (repeated measures pre versus post ANOVA: $F(1,13) = 69.125$; $p < 0.0001$, pre-post difference t test $p < 0.0001$), but thresholds of the not coactivated IF of the left hand remained unchanged (pre, 1.53 ± 0.24 mm; post, 1.50 ± 0.24 mm; repeated measures ANOVA: $F(1,13) = 1.128$; $p = 0.308$, pre-post difference t test $p = 0.3$, Figure 2B). We reinvestigated the recovery of coactivation in four subjects. The present findings corroborate those of earlier studies (Godde et al., 1996, 2000; Pleger et al., 2001; Dinse et al., 2003): 24 hr after coactivation, we found normal 2-point discrimination thresholds similar to those obtained prior to coactivation (1.55 ± 0.26 mm [mean ± SD]; Figure 2A).

To demonstrate the Hebbian nature of the coactivation protocol, we compared the effects of coactivation with a so-called single-site stimulation in 16 subjects (7

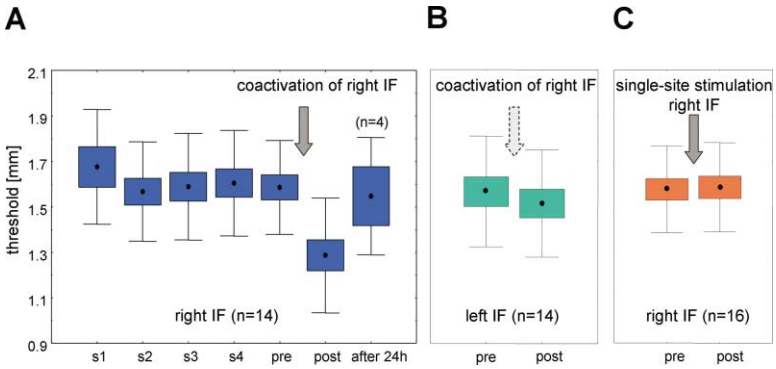

Figure 2. Psychophysical Effects of Coactivation

(A) Effects of coactivation on discrimination thresholds. Average data from all subjects (n = 14). Dots represent mean thresholds, boxes show the standard errors, and whiskers correspond to the standard deviation. Coactivation period (3 hr) of the right IF is indicated by arrows. Left: shown are results from five consecutive sessions before coactivation of the right index finger (IF). After the session S5 (precondition), coactivation was applied. After coactivation, discrimination thresholds were significantly reduced.

(B) Discrimination thresholds obtained for the control finger (IF of the left hand that was not coactivated) for the pre- and postcondition. Note lack of effects after coactivation of the right IF (postcondition), indicating finger specificity of the coactivation protocol. 24 hr after coactivation, we found normal 2-point discrimination thresholds similar to those obtained prior to coactivation.

(C) Effects of single-site stimulation on discrimination thresholds. Average values from 16 subjects obtained for the right IF pre and post single-site stimulation. Same conventions as in (A). We found no changes of discrimination thresholds after 3 hr of stimulation.

male, 9 female, all right-handed, mean age 26.3 ± 3.66 years), where only a small "point-like" skin area was stimulated. Otherwise, stimulation frequency and duration of stimulation period were the same as described for coactivation. All subjects achieved a stable 2-point discrimination performance as estimated from repeated assessment of thresholds over five consecutive sessions. However, stimulating for 3 hr the tip of the right IF with a single site only led to no changes of thresholds (pre, 1.57 ± 0.27 mm [mean ± SD]; post, 1.58 ± 0.27 mm, repeated measures pre versus post ANOVA: $F(1,15) = 0.735$, $p = 0.408$; Figure 2C). For individual subject psychometric curves, see Figure 5. These results imply that "co"-activation is crucial for the induction of the effects. Furthermore, we calculated the signal detection d' value, which is a bias-free discrimination index (Wickens, 2002), as well as the false alarm and hit rates (see Experimental Procedures). After coactivation, we found an increase of the d' value from 2.33 ± 0.29 (mean ± SD) to 3.25 ± 0.42, indicating enhanced discrimination abilities. In contrast, d' values before and after single-site stimulation remained unchanged (pre, 2.78 ± 0.78; post, 2.94 ± 0.52). Comparing false alarm rates before and after coactivation (pre, 0.03 ± 0.02; post, 0.01 ± 0.01) and single-site stimulation (pre, 0.02 ± 0.03; post, 0 ± 0) revealed that they remained unchanged. However, hit rates increased after coactivation (pre, 0.66 ± 0.08; post, 0.81 ± 0.04) but not after single-site stimulation (pre, 0.65 ± 0.03; post, 0.66 ± 0.05).

Effects of Coactivation on BOLD Signal

For fMRI data analysis, we used the Statistical Parametric Mapping (SPM) software. The result of the group analysis shown in the estimated statistic parametric map of the precoactivation session revealed focused SI activation in the postcentral gyrus. In addition, we found a broad SII activation contralateral and ipsilateral to the stimulated IF in the parietal operculum above the Sylvian fissure (Figures 3A and 3B, see Figure 4A for an individual data set; for a summary of all individual fMRI data, see Tables 1 and 2). For each subject, the coordinates of maximal BOLD activity (see Table 1) could be assigned to either SI or SII according to the Talairach atlas (Talairach and Tournoux, 1988). After coactivation, for both SI and SII contralateral to the stimulated IF, we found an enlargement of activation pattern and an enhancement of the amplitude of the BOLD signal (Figures 3C and 3D, Tables 1 and 2, Figure 4A for an individual data set). According to the random-effect analysis, significantly activated areas were only localized in SI and SII contralateral to the stimulated IF (Figure 3E). A lack of changes in BOLD activity was found contralateral to the control IF of the left hand (Figure 3F). A linear correlation analysis between the normalized number of activated voxels $\boldsymbol{K}$ ($\boldsymbol{K} = ((\text{right}_{post} - \text{right}_{pre}) - (\text{left}_{post} - \text{left}_{pre}))/\text{right}_{pre}$) for SI and SII revealed a lack of relationship ($r = -0.55$, $p = 0.851$).

To analyze the spatial distribution of the activated pattern, we calculated the centers of cluster gravity (CoG) before and after coactivation. The comparison of the Euclidean distance between the pooled pre-post CoG indicated a lateral shift by 11.9 mm for contralateral SI (compare red marker position in glass brain view of Figures 3A and 3D). Parallel to the recovery seen in the psychophysical data, the effects of coactivation on BOLD signals in SI and SII were reversible 24 hr after coactivation (Figure 4, Table 2).

In six subjects, we additionally measured BOLD signals before and after single-site stimulation. For a single subject data set together with its psychometric performance, see Figure 5. Comparing pre with post single-site stimulation fMRI session revealed no significant changes in BOLD signal extension and intensity in SI and SII contralateral to the stimulated IF. These results confirm that tactile stimulation of the tip of the IF over several hours had no effects, either psychophysically or cortically.

Correlation between Perceptual and BOLD Signal Changes

To elucidate the relationship between coactivation-induced changes in BOLD signals and the individual perceptual changes in discrimination thresholds, we performed a correlation analysis. This analysis showed a close link between individual gain in performance and the degree of reorganizational changes, which was restricted to the contralateral SI digit representation (Figure 6A). In contrast, no comparable correlation was found between changes in individual performance and reorganization within SII. These findings were corroborated by calculating Pearson's linear correlation coefficients between cortical enlargement (normalized number of activated voxels $\boldsymbol{K}$) and psychophysical threshold reduction (Figure 6B).

Discussion

Combining fMRI imaging with psychophysical assessment of discrimination thresholds demonstrates that the involvement of somatosensory cortex in fast perceptual learning is not restricted to SI but extends equally well to the next hierarchical level at SII (Figures 3 and 4, Tables 1 and 2). fMRI is widely used to study the organization of the human brain during operation by measuring the BOLD signal, which makes use of the close link between energy metabolism and neural activation. To understand the relative contribution of several types of neuronal signals to the hemodynamic response, local field potentials and single- and multi-unit activity have been compared to high spatiotemporal fMRI responses recorded simultaneously in monkey visual cortex (Logothetis et al., 2001). Only local field potentials were significantly correlated with the hemodynamic response, indicating that BOLD signals primarily measure the input and processing of neuronal information within a region of cortex and not the output (Logothetis, 2002; Logothetis et al., 2001).

Coactivation Protocol

The coactivation is a task-free, passive stimulation protocol. It was developed to study systematically the impact of altered input statistics on plastic capacities of cortical networks. The protocol induces cortical reorganization without invoking task training or cognitive factors such as attention or reinforcement. Many studies have demonstrated that plastic cortical changes can be

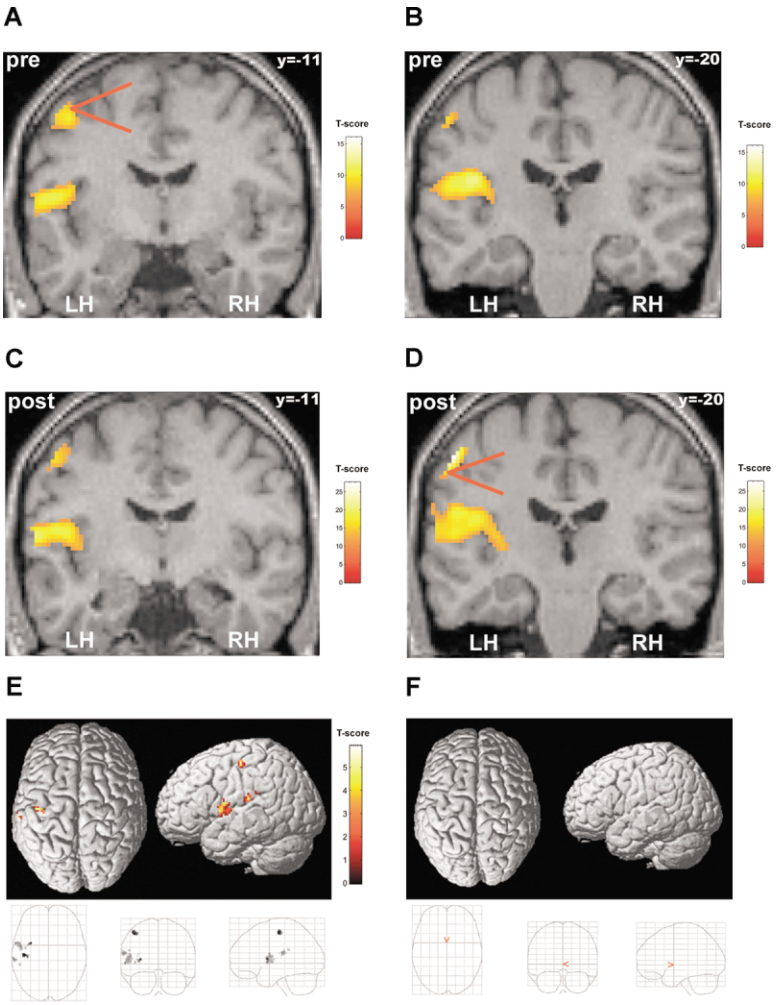

Figure 3. Cortical Effects of Coactivation

(A–D) Fixed-effects analysis shows BOLD signals detected pre (A and B) and post (C and D) coactivation in the contralateral SI and in the contralateral and ipsilateral SII. Coronar slices are viewed from the back (LH, left hemisphere; RH, right hemisphere; y values, MNI coordinates). Activations are projected on coronal T1-weighted MRI slices. (A and B) Precoactivation. S1 parameters: cluster level = 255 v(oxels); T-score = 10.12; MNI template coordinates (mm) = −46, −11, 50 (x,y,z); S2 (contralateral) parameters: 2316 v; T-score = 12.34; −48, −28, 20 (x,y,z); S2 (ipsilateral) parameters (not shown): 382 v; T-score = 11.23; 57, 2, 8 (x,y,z). (C and D) Postcoactivation. S1 parameters: 1091 v; T-score = 20.23; −56, −21, 50 (x,y,z); S2 (contralateral) parameters: 4354 v; T-score = 23.34; −46, −30, 20 (x,y,z); S2 (ipsilateral) parameters (not shown): 562 v; T-score = 11.99; 52, 4, 8 (x,y,z). In order to obtain information about the spatial distribution of the activated pattern, we additionally calculated the centers of cluster gravity (CoG) before and after coactivation: SI pre, −48, −11, 53 (x,y,z); post, −54, −20, 48 (x,y,z); SII (contralateral) pre, −47, −22, 18 (x,y,z); post, −48, −20, 14 (x,y,z); SII (ipsilateral) pre, 56, 2, 4 (x,y,z); post, 54, −6, 8 (x,y,z). The comparison of the Euclidean distance between the pooled pre-post CoG indicated a lateral shift by 11.9 mm for contralateral SI (compare red marker position) and a medial shift of 9.17 mm for ipsilateral SII. Although contralateral SII signals were also significantly enlarged, the Euclidean distance pre-post CoG showed a lateral shift of only 4.58 mm.

(E) Random-effect analysis (paired t test pre versus post, right IF) revealed significant changes of activated patterns localized in SI and SII contralateral to the coactivated IF (threshold: $p = 0.001$; uncorrected for multiple comparisons; S1 parameters: 22 v; T-score = 5.92; −44, −18, 54 (x,y,z); S2 parameters: three main patterns of activation: (1) 26 v; T-score = 4.5; −60, −26, 20 (x,y,z); (2) 12 v; T-score = 4.37; −38, −22, 14 (x,y,z); (3) 98 v; T-score = 3.83; −50, −4, 4 (x,y,z).

(F) No changes of BOLD activity were found contralateral to the control IF of the left hand (paired t test pre versus post; threshold: $p = 0.001$, uncorrected for multiple comparisons).

evoked by variation of input statistics alone, provided the statistics are sufficiently altered (Diamond et al., 1993; Kilgard et al., 2002; Liepert et al., 1999). For example, perceptual learning occurs even without awareness by repetitive exposure to stimuli that are below the threshold of visibility and that are irrelevant to the central task (Watanabe et al., 2001).

Coactivation as used in the present study follows closely the idea of Hebbian learning: synchronous neural activity, which is regarded as instrumental to drive plastic changes, is generated by the simultaneous tactile "costimulation." Conceivably, coactivation modifies synaptic efficacy between and within the cortical neuron pool representing the IF; for an account showing that dendritic spikes mediate a form of synaptic potentiation that does not require postsynaptic action potential firing in the axon, see Golding et al. (2002). As a chain of changes, we suggest that the simultaneous activation on the skin alters synaptic transmission at a cortical level, which results in an enlargement of the finger representation in SI (Pleger et al., 2001; Dinse et al., 2003) and SII. However, at present, little is known about how cortical map changes translate to changes of discrimination performance. According to our data, enlargement of cortical territory in SI is linearly correlated with a lowering of spatial discrimination thresholds (Figure 6). Several years ago, animal studies demonstrated a significant correlation between the enlargement of cortical territory and the improvement in performance (Recanzone et al., 1992, 1993). Interestingly, clinical studies showed that the degree of cortical maladaptations was related to the degree of associated changes of behavior (Flor et al., 1995; Traversa et al., 1997). What the present and the previous studies have in common is the demonstration of a proportionality between performance and cortical territory. In other words, recruitment of cortical processing resources appears to be crucially involved in mediating superior performance. Conceivably, small differences in performance may not necessarily be due to measurement artifacts or noise, but may reflect true

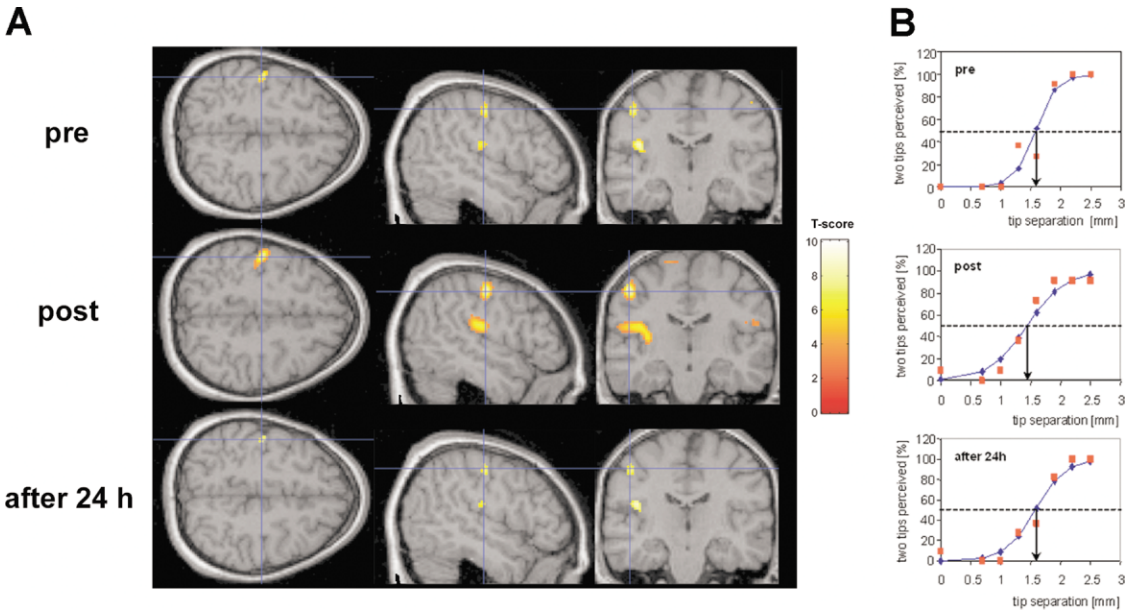

Figure 4. Single Subject Coactivation Effect

(A) BOLD signals detected pre, post, and 24 hr after coactivation in the contralateral SI in the postcentral gyrus and in the contralateral SII in the parietal operculum above the Sylvian fissure. Activations are projected on an axial (left), saggital (middle), and coronar (right) T1-weighted, normalized MRI slice. Comparing pre- with postcoactivation fMRI sessions revealed enlarged activation and increased BOLD signal intensity in SI and SII contralateral to the coactivated IF. The slight increase in ipsilateral SII found in this subject and in several others did not reach significance level in the group analysis. These changes of BOLD signal characteristics recovered 24 hr after coactivation was applied. For individual parameters, see Table 1 (subject 1). According to the single-subject analysis, no multiple activation peaks were found in SII, as shown in this example.

(B) Psychometric functions illustrating the coactivation-induced improvement of discrimination threshold for the subject shown in (A). Correct responses in percent (red squares) are plotted as a function of separation distance together with the results of a logistic regression line (blue with blue diamonds). 50% levels of correct responses are shown as well as thresholds. Top, precondition before coactivation; middle, postcondition, immediately after coactivation; bottom, recovery after 24 hr. After coactivation there is a distinct shift in the psychometric functions toward lower separation distances by 0.14 mm, which recovers to preconditions 24 hr later.

differences in individual brain organization. However, in deprived animals the amount of active exploration appeared to determine the direction of plastic changes, suggesting that exceptions from that rule might exist (Polley et al., 1999).

It is unlikely that unspecific factors such as overstimulation or coactivation-induced hypersensitivity might cause systematic changes in 2-point discrimination. According to unpublished data, absolute touch thresholds as assessed using von Frey hairs remained unchanged after 3 hr of coactivation. As a control, to show the Hebbian nature of the coactivation effects, we used a modified version of the coactivation protocol consisting of a single small stimulation site instead of one large area (50 mm^2 versus 0.8 mm^2). When this protocol was applied for 3 hr to the tip of the right IF, no effects, either on discrimination or on cortical maps in SI and SII, were found (Figure 5), indicating that "coactivation" is indeed crucial. These findings also make it rather unlikely that general processes such as attentional enhancement were involved. The increase of the discrimination index (d' value) provides further support for the specificity of the coactivation effect.

It should be noted that we additionally explored the effects of a protocol of so-called uncorrelated coactivation using two independent small stimulators (separation 5 mm) driven by two independent Poisson processes. Under these conditions, simultaneity occurs by chance. Synchronous coactivation lowered thresholds as described here. In contrast, uncorrelated coactivation did not cause no effects, but instead revealed a significant impairment of tactile performance (H.R. Dinse et al., 2002, Soc. Neurosci., abstract). In parallel, we made electrophysiological recordings in rats comparing a correlated and an uncorrelated coactivation mode. These data showed that manipulating input correlations resulted in complementary forms of cortical map reorganization. In addition, responsiveness of cortical neurons was potentiated after correlated, but depressed after uncorrelated, coactivation (H.R. Dinse et al., 2002, Soc. Neurosci., abstract). According to these data, uncorrelated coactivation is not a genuine "control," but a new and different way to induce perceptual learning.

Due to the task-free nature of coactivation, it is reasonable to assume that coactivation alters the entire way sensory information is processed. However, fundamental changes of tactile information processing do not rule out that some aspects of tactile information processing might deteriorate. According to unpublished data, tactile localization on the IF became worse after coactivation. A similar trade-off between localization and dis-

Table 1. Individual fMRI Data

			SI Activity Contralateral to Coactivated Index Finger			SII Activity Contralateral to Coactivated Index Finger						
							Maximum of Activity		Second submaximum of Activity		Third submaximum of Activity	
Subject	Coactivation	Height Threshold (T)	Cluster Level of SI Activity in Left Hemisphere (k_E)	MNI Coordinates (x,y,z in mm) of SI Pattern	Voxel Level, T-Score, SI Activity	Summed Cluster Level of SII Activity in Left Hemisphere (k_E)	MNI Coordinates (x,y,z in mm) of SII Pattern	Voxel Level, T-Score, SII Activity	MNI Coordinates (x,y,z in mm) of SII Pattern	Voxel Level, T-Score	MNI Coordinates (x,y,z in mm) of SII Pattern	Voxel Level, T-Score
1	pre	6.83	51	−50, −22, 50	12.08	372	−36, −20, 18	10.03	−46, −26, 22	9.87	−56, −26, 20	8.84
	post	6.83	174	−52, −22, 50	12.32	946	−38, −18, 20	18.47	−44, −28, 20	14.25	−62, −26, 20	13.82
2	pre	3.13	13	−56, −22, 52	4.09	139	−38, −26, 2	4.86	−46, −10, 14	4.04	−38, −16, 12	3.9
	post	3.13	103	−56, −24, 52	8.32	85	−36, −10, 22	7.11	−34, −16, 8	5.52	-	-
3	pre	5.33	15	−48, −10, 58	6.4	219	−44, −38, 20	8.43	−54, −32, 14	7.02	−64, −28, 14	6.89
	post	5.33	199	−42, −18, 50	8.8	357	−54, 6, 2	8.85	−58, −4, 10	8.02	−52, −10, 14	7.81
4	pre	5.86	40	−48, −12, 60	7.44	60	−52, 0, 6	7.94	-	-	-	-
	post	5.8	208	−40, −12, 64	13.32	113	−54, −2, 8	13.08	−46, −22, 14	12.98	−46, 0, 4	12.62
5	pre	3.13	61	−54, −20, 46	4.18	42	−56, 0, 14	4.09	-	-	-	-
	post	3.13	197	−54, −20, 46	4.18	158	−38, −20, 16	4.18	−56, 0, 14	4.09	−48, −8, 6	3.92
6	pre	3.13	19	−52, −14, 54	4.5	70	−50, −26, 20	4.11	−52, −10, 14	3.95	-	-
	post	3.13	50	−64, −38, 40	4.42	32	−50, −24, 22	3.78	−52, −8, 12	3.55	−54, −18, 12	3.42
7	pre	3.79	20	−56, −12, 50	4.91	477	−52, −18, 20	6.95	−42, −14, 14	6.32	-	-
	post	3.79	69	−56, −16, 50	6.37	684	−42, −16, 14	6.52	−36, −10, 6	5.03	-	-
8	pre	4.95	142	−52, −12, 56	9.23	689	−44, −30, 24	10.89	−66, −32, 22	9.1	−36, −22, 16	7.05
	post	4.97	304	−48, −12, 56	9.2	2123	−44, −30, 22	13.55	−36, −22, 14	11.35	−62, 30, 26	10.9
9	pre	6.84	238	−44, −6, 48	13.81	511	−52, 4, 0	11.46	−58, −14, 12	10.3	−44, −22, 20	9.87
	post	6.8	467	−42, −6, 48	12.8	326	−60, 10, −2	11.28	−52, −26, 6	7.2	-	-
10	pre	4.96	37	−54, −26, 54	8.75	837	−52, −30, 16	12.42	-	-	-	-
	post	4.96	50	−54, −24, 54	9.63	899	−42, −26, 20	12.04	−52, −30, 12	10.16	−54, −32, 22	9.53

This table shows the cluster level and the voxel level of activity pattern in primary (SI) and secondary (SII, cluster of maximum activity and the two main submaximums of activity) somatosensory cortex pre- and postcoactivation.

Table 2. Recovery Measurements in Four Subjects

			Recovery Measurements: SI and SII Activity Contralateral to the Coactivated Index Finger (Pre, Post, and 24 Hours after Coactivation)								
			(1) Precoactivation			(2) Postcoactivation			(3) 24 Hours after Coactivation		
Subject	Cortex	Height Threshold (T)	Cluster Level of Activity in Left Hemisphere (k_E)	MNI Coordinates (x,y,z in mm) of Activated Pattern	Voxel Level, T-Score	Cluster Level of Activity in Left Hemisphere (k_E)	MNI Coordinates (x,y,z in mm) of Activated Pattern	Voxel Level, T-Score	Cluster Level of Activity in Left Hemisphere (k_E)	MNI Coordinates (x,y,z in mm) of Activated Pattern	Voxel Level, T-Score
1	SI	6.83	50	−48, −20, 50	7.76	187	−50, −18, 48	10.42	36	−48, −21, 51	7.05
	SII		115	−42, −22, 20	10.05	641	−45, −24, 19	11.83	93	−40, −22, 20	9.85
2	SI	8.47	90	−44, −6, 50	12.84	143	−46, −6, 48	13.41	75	−46, −8, 46	13.41
	SII		88	−44, −24, 20	9.49	227	−44, −22, 22	10.08	140	−44, −24, 22	9.99
3	SI	9.22	40	−56, −10, 48	15.84	246	−54, −6, 46	13.36	45	−54, −12, 52	12.55
	SII		46	−64, −42, 14	13.86	118	−60, −22, 6	11.76	71	−58, −18, 10	10.79
4	SI	5.21	45	−52, −24, 54	7.76	84	−52, −22, 54	8.76	39	−52, −12, 52	7.42
	SII		342	−54, −32, 16	11.04	455	−54, −24, 20	13.36	316	−54, −26, 18	10.98

This table shows the SI and SII activity contralateral to the coactivated index finger pre, post, and 24 hr after coactivation.

crimination has been shown in a study of Braille readers (Sterr et al., 1998). Conceivably, enhanced spatial discrimination appears to emerge in parallel to impaired localization. For a detailed discussion of the influence of stimulus numbers, see Pleger et al. (2001).

SI Reorganization

Cortical maps are in a permanent state of use-dependent fluctuations. According to animal studies, map size is a reliable predictor of individual performance. Evidence in humans is mostly indirect, resulting from calculating the positions of current sources. For SI reorganization, our data revealed a linear relationship between the degree of learning-induced perceptual improvement and the degree of reorganization. Using the method of fMRI imaging, we uncovered focused pattern of activation within SI, representing the correlation with the individual perceptual improvement (Figure 6). Accordingly, little gain in discrimination abilities was associated with small changes in BOLD signals, but subjects, who showed a large cortical reorganization, also had a high gain in discrimination.

These data confirm previous mapping studies in human SI using somatosensory-evoked potentials (SSEP) (Pleger et al., 2001; Dinse et al., 2003): individually observed reorganization of SI was inferred from lateral shifts of the N20-dipole localization of the IF, which were linearly correlated with the parallel changes in spatial 2-point discrimination thresholds. Using fMRI, we found a similar lateral shift for the center of gravity (Figures 3A–3D). This data demonstrates that following coactivation, a lateralization of the N20-dipole together with an increase in dipole strength is compatible with an enlargement of cortical representational maps as described in the animal studies (Godde et al., 1996). Using fMRI, we are now able to directly show the enlargement of cortical territory together with a lateral shift of BOLD signals as a consequence of coactivation, which provides further evidence for the correctness of the interpretation of dipole shifts inferred from SSEP mapping (Pleger et al., 2001; Dinse et al., 2003). Accordingly, the reorganization of the cortical representation of the IF in SI after coactivation on the tip of the IF consists of an asymmetric lateral enlargement toward the representation of the thumb, while the position of maximal activation remains at the location of the IF as mapped under control conditions.

SII Reorganization

Besides the performance-dependent enlargement of SI, we found that localized reorganizational changes can be induced at the next hierarchical level at SII. While lesion-induced reorganization has been observed outside SI (Pons et al., 1988), learning-induced plastic changes have so far not been described for SII. In amputees, neuroelectric source imaging revealed decreased activity in ipsilateral SII cortex associated with nonpainful phantom sensation (Flor et al., 2000). Using fMRI, an enlarged bilateral SII representation of a telescoping perception of the phantom limb was reported (Condes-Lara et al., 2000). In our study, under control conditions, the patterns of SII activation were variable across subjects, indicating a less consistent somatotopic organization of SII (Tables 1 and 2; Del Gratta et al., 2000; Disbrow

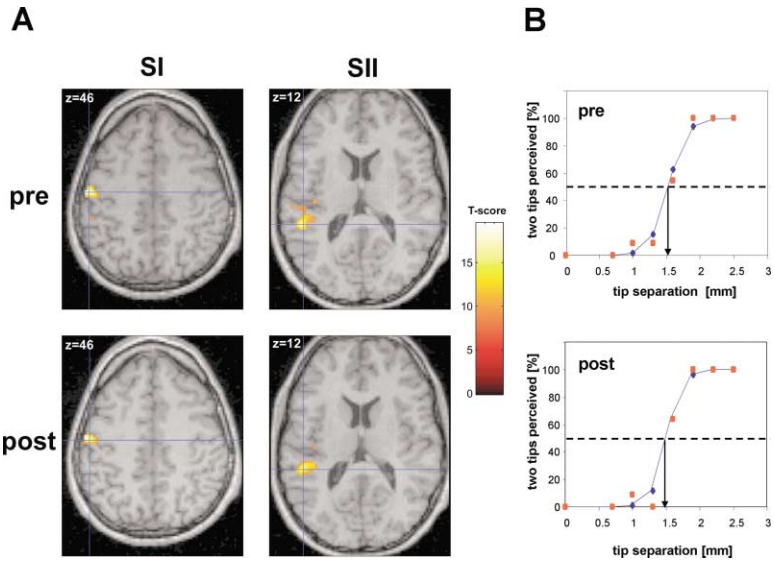

Figure 5. Single-Site Stimulation Effects

(A) BOLD signals detected pre and post single-site stimulation in the contralateral SI and SII in one subject. Activations are projected on axial T1-weighted, normalized MRI slices. Comparing pre with post single-site stimulation fMRI session revealed no substantial changes in BOLD signal extension and intensity in SI and SII contralateral to the stimulated IF (SI pre: cluster level = 261 v(oxels), T-score = 19.5; post: 281 v, T-score = 19.4; SII (contralateral) pre: 236 v, T-score = 17.2; post: 191 v, T-score = 15.9). Group data (n = 6) is as follows. SI pre: mean cluster level = 89 v (SEM ± 36.1 v), mean T-score = 11 (± 1.9); post: 96 v (± 38.7 v; Student's paired t test pre versus post: p = 0.6), T-score = 12 (± 2; pre versus post: p = 0.7); SII (contralateral) pre: 230 v (± 138.9 v), T-score = 9 (± 2.2); post: 176 v (± 107 v; pre versus post: p = 0.2), T-score = 9 (± 2.1; pre versus post: p = 0.17).

(B) Psychometric functions illustrating discrimination performance obtained pre and post single-site stimulation for the subject shown in (A). Correct responses in percent (red squares) are plotted as a function of separation distance together with the results of a logistic regression line (blue with blue diamonds). 50% levels of correct responses are shown as well as thresholds. Top: precondition before single-site stimulation; bottom: postcondition, immediately after single-site stimulation (prethreshold, 1.52 mm; postthreshold, 1.49 mm).

et al., 2000; Ruben et al., 2001; Simoes et al., 2001). According to the random-effects analysis, no statistically significant pattern was found in SII ipsilaterally (Figure 4E).

The missing correlation between SII enlargement and the degree of discrimination improvement does not rule out that SII is not involved in this task. According to a recent fMRI study, no separated representations of the index and fifth fingers were found in SII (Ruben et al., 2001). Similarly, substantial functional overlap of finger representations for human SII has been reported using high-resolution MEG (Simoes et al., 2001). Conceivably, the lack of fine-grained somatotopy together with the substantial variability in activation might explain the lack of correlation between individual reorganization in SII and changes of discrimination thresholds. The enlargement of the digit representation in SII after coactivation constitutes a recruitment of processing resources, suggesting a crucial role in processes related to improved discrimination abilities as suggested by other studies (Romo et al., 2002).

In conclusion, the concept of Hebbian learning has

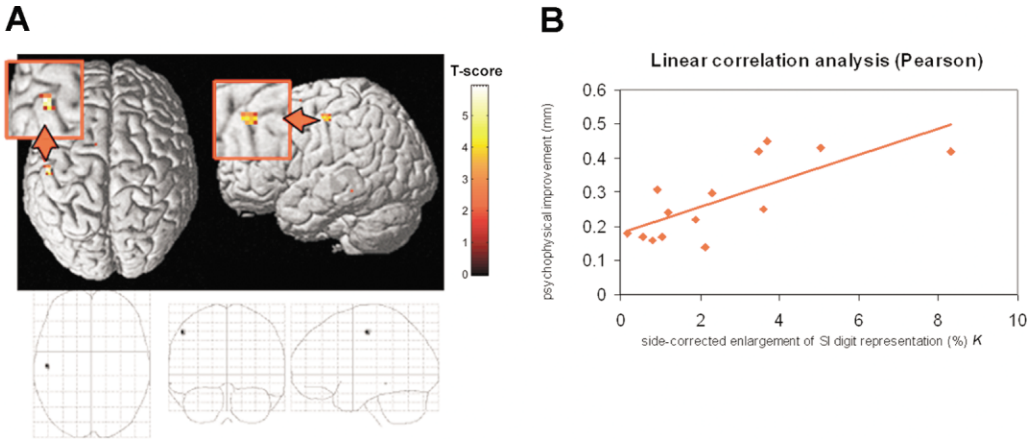

Figure 6. Correlation Analysis

Relationship between changes in BOLD signals and coactivation induced changes of two-point discrimination thresholds (A). Results revealed a significant correlation between perceptual and cortical changes within SI on the postcentral gyrus (see also magnified detail). In contrast, no activated clusters were found within SII. (threshold: p = 0.001; uncorrected for multiple comparisons; v(oxel) = 2 mm^3; S1 parameters: cluster level = 14 v; T-score = 4.82; −52, −16, 50 (x,y,z). Linear correlation analysis between perceptual and cortical changes in SI (Pearson) (B) corroborated these findings. To express the effect of tactile coactivation on BOLD signals of the contralateral SI, we used the corresponding number of activated voxels per cluster: $K = ((right_{post} - right_{pre}) - (left_{post} - left_{pre}))/right_{pre}$. "$K$" was correlated with coactivation-induced changes in psychophysical thresholds (r = 0.744; p = 0.002). We found no significant correlation between perceptual and plastic changes in SII (r = 0.08; p = 0.979).

been proven to be one of the most productive paradigms in neurosciences. While studies describing molecular and cellular mechanisms of synaptic learning are in line with the Hebbian ideas, data linking Hebbian learning to altered perception are rare. Our results show that fMRI is a valuable tool for demonstrating the implications of fast perceptual learning based on Hebbian mechanisms for cortical reorganizational changes within distributed networks, which are correlated with changes of the individual percept.

Experimental Procedures

Experimental Schedule

The experiments consisted of four different components: (1) the measurement of 2-point discrimination thresholds on the tip of the left and right index finger (IF) as an indirect marker of cortical reorganization and as an indicator for the perceptual relevance of the coactivation protocol; (2) fMRI measurements of BOLD images evoked by electrical stimulation of the left and right IF; (3) the coactivation of 3 hr duration to induce cortical reorganization on the tip of the right IF (Figure 1A); and (4) a control consisting of a single-site stimulation.

As a rule, the IF of the right hand was used for coactivation. To obtain a stable baseline of discrimination, we tested the subjects on five consecutive sessions on the right IF. Sessions were statistically analyzed for stability (ANOVA). In the fifth session, the thresholds of the left IF were additionally measured. Previous studies had shown that the coactivation effect to the right IF did not transfer to the IF of the left hand (Godde et al., 1996, 2000; Pleger et al., 2001; Dinse et al., 2003). We therefore used the IF of the left hand as a control and for the assessment of possible unspecific side effects of coactivation. In addition, the comparison of the thresholds of the left IF pre-post ruled out the electrical stimulation during the fMRI session having an effect on either the performance or the cortical representation. Finally, the single-site stimulation on the right IF of 3 hr duration rules out that unspecific factors such as attentional facilitation are unlikely to contribute to the coactivation effects.

After the assessment of discrimination performance of both the test and the control finger (precondition), subjects were subjected to fMRI measurements to obtain the pre-activation pattern (Figure 1A). Then coactivation was applied to the right IF (Figure 1B). Discrimination performance of the IF of each hand was retested starting about 30 min after the termination of the coactivation protocol (postcondition). Then fMRI measurements were repeated to assess post-activation pattern. Previous studies had shown complete reversibility of coactivation-induced changes in discrimination performance and in dipole localization after the termination of coactivation (Godde et al., 1996, 2000; Pleger et al., 2001, Dinse et al., 2003). In the present study, we investigated the recovery of coactivation-induced changes in four subjects perceptually and by using fMRI (seventh session, Figure 1A).

Measurement of 2-Point Discrimination Thresholds

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 the Ruhr-University Bochum.

We tested 14 right-handed subjects (4 male, 10 female; mean age 31.6 years, SD $\pm$ 3.7 years) in a 2-alternative forced-choice simultaneous spatial 2-point discrimination task (Godde et al., 1996, 2000; Pleger et al., 2001; P. Ragert et al., 2001, Soc. Neurosci., abstract; Dinse et al., 2003). Seven pairs of needles were mounted on a rotatable disc that allowed us to switch rapidly between distances. 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 and zero distance was tested with a single needle.

To accomplish a rather uniform and standardized type of stimulation, the disc was installed 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 down movement was arrested by a stopper at a fixed position above the needles. The test finger was held in a hollow containing a small hole through which the finger touched the needles at approximately the same indentation in each trial. Each distance of the needles was tested 10 times in randomized order, resulting in 80 single trials per session, which lasted about 15 min. Without being given feedback, the subject had to decide immediately if he had the sensation of one or two tips by answering "one" or "two." The subjects had been instructed that there were single needle presentations for control, but not how often. Thus, there was no knowledge available to the subjects that could be used as a strategy to bias the decisions.

The summed responses were plotted against distance as a psychometric function for absolute threshold, fitted by a binary logistic regression (SPSS, SPSS Inc.). Threshold was taken from the fit at the distance where 50% correct responses was reached. To provide a direct experimental test for a bias-free discrimination index, we additionally carried out psychophysical tests, where we presented as many single needles as double needle presentations. We did this by increasing the number of single needle presentations to 70 (70 single, 70 double needle presentations), resulting in a session with a total of 140 presentations. From these data we calculated the false alarm as well as the hit rates and the discrimination index (d' value) (Wickens, 2002).

Coactivation

The coactivation protocol was the same as in our previous studies (Godde et al., 1996, 2000; Pleger et al., 2001; P. Ragert et al., 2001, Soc. Neurosci., abstract; Dinse et al., 2003). The basic idea behind this design was to coactivate a large number of receptive fields in a Hebbian manner in order to strengthen their mutual interconnectedness. Coactivation stimuli were presented at different interstimulus intervals from 100 to 3000 ms in pseudorandomized order; average stimulation frequency was 1 Hz and the duration of each pulse was 10 ms. Pulses were recorded on tape and were played back via portable tape recorders, allowing unrestrained mobility of the subjects during coactivation. Subjects were instructed not to attend the stimulation. In fact, all subjects resumed their normal day's work. To apply coactivation, a small solenoid with a diameter of 8 mm was taped to the tip of the right index finger and transmitted the tactile stimuli of the coactivation protocol to the skin. The solenoid allowed simultaneous stimulation of the skin portions of the index finger under the solenoid, leading to coactivation of all receptive fields within this area, for an estimate of receptive field sizes of the human index finger see (Figure 1B; Vega-Bermudez and Johnson, 1999). According to this data, receptive fields within 8 mm of the tip of the index finger overlap partially or are nonoverlapping. Discrimination pre-post was always tested inside the coactivated skin area. Coactivation stimuli were applied at suprathreshold intensities. Duration of coactivation was 3 hr.

Single-Site Stimulation

To provide a control for the Hebbian nature of the coactivation and to rule out that unspecific factors are unlikely to contribute to the coactivation effects, we applied a so-called single-site stimulation. For that purpose, we used a tiny stimulator that was also taped to the tip of the right IF. The device consisted of a small probe (diameter 0.5 mm) that was moved up and down by means of a small relay (Figure 1C). In that way, a single "point" (0.8 mm^2) was stimulated instead of coactivating a large area of 50 mm^2. Stimulation parameters were identical to those used for coactivation: pulse duration was 10 ms and average frequency was 1 Hz using interstimulus intervals from 100 to 3000 ms in pseudorandomized order. Duration of single-site stimulation was 3 hr.

fMRI Scanning

fMRI measurement was performed with a whole-body 1.5 T scanner (Magnetom Symphony, Siemens Medical Systems, Germany) equipped with a high-power gradient-system (30 mT/m/s; SR 125 T/m/s), using a standard imaging head coil. Blood-oxygen level-dependent (BOLD) images were obtained with a single-shot SpinEcho-EPI sequence (TR 1600 ms, TE 60 ms, matrix 64 $\times$ 64, field of view [FOV] 224 mm, 5 mm slice thickness, 1 mm gap between slices, voxel 3.5 $\times$ 3.5 $\times$ 5 mm). We acquired 16 transaxial slices parallel to the

AC-PC line, which covered the whole brain excluding cerebellum. Ten subjects were examined before and after coactivation.

For finger stimulation we used a TENS stimulator (Medicommerz, Kirchzarten, Germany) with conventional ring-electrodes (medco) mounted on the tip of the index finger. For comparability of the fMRI data with previously published SSEP (somatosensory evoked potentials) data (Pleger et al., 2001; Dinse et al., 2003), we chose an identical stimulation protocol as used in the SSEP studies: pulse duration was 0.1 ms and repetition rate 3 Hz. Stimulation intensity was adjusted to 2.5 times above sensory threshold. Electrodes were removed between sessions, but position on the fingers was marked to make sure that the same skin positions were stimulated. Each activation study comprised nine blocks of rest and eight blocks of stimulation, each of which contained 40 scans. Subjects were instructed to keep their eyes closed and to concentrate on stimulation during the whole session. BOLD activation after electrical stimulation of the IF of each hand was measured in separate sessions that were counterbalanced. Anatomical images were acquired using an isotropic T1-3dGE (MPRAGE) sequence (TR 1790 ms, TE 388 ms, matrix 256×256, FOV 256 mm, 1 mm slice thickness, no gap, voxel size: $1 \times 1 \times 1$ mm) with 160 sagittal orientated slices covering the whole brain.

Data Analysis

For preprocessing and statistical analysis of fMRI data, we used the Statistical Parametric Mapping (SPM) software package, version 99 (Wellcome Department of Cognitive Neurology, London, UK) in batch mode running under the MATLAB R12 environment (Mathworks Inc., Sherborn, MA). The first 10 images of each fMRI session (690 images), during which the BOLD signal reaches steady state, were discarded from further analysis. We measured both IFs in separate sessions in pre and post conditions. First, all scans were realigned and a mean image in the process was formed. Scans were resliced using Sinc interpolation. Sessions in which movements exceeded 2 mm in any direction were removed from further analysis. The individual three-dimensional data sets were normalized using the standard template of the Montreal Neurological Institute (MNI) (voxel size, 2 mm^3) to establish an interindividual comparability (Geyer et al., 2000). Scans were smoothed with a 6 mm (full-width half-maximum) isotropic, three-dimensional Gaussian filter. Statistical maps were calculated using a high-pass cut-off at 256 s, a hemodynamic response function (hrf; lowpass filter), and a threshold of $p = 0.05$ (corrected for multiple comparisons). SPM contrast was used for each subject and session separately. For the topographic assignment of BOLD signals of the different measurements, we coregistered the mean image formed in a realignment procedure with the anatomic image from the T1-GE sequence scan. Statistical parametric maps of group analysis were generated to identify localization, cluster level, center of cluster gravity (CoG), MNI coordinates, and spatial magnification of activated patterns.

Group analysis (fixed-effect model) was performed on all tested subjects pre- and postcoactivation (Friston et al., 1999; Poldrack, 2000). Significance was determined using $p = 0.001$ for peak height and corrected for multiple comparisons. To evaluate differences of pre- and postcoactivation sessions, we performed a random-effect analysis using Student's paired t test of right and left sides separately. To analyze the relationship between coactivation-induced changes in BOLD signals and the individual perceptual changes in discrimination thresholds, we performed a simple correlation analysis. The effect of coactivation on BOLD signals was expressed by side-corrected difference maps for each individual subject. The differences in thresholds before and after coactivation (post − pre) were inserted as covariates. Linear correlation analysis (Pearson) between individual pre- and post-coactivation maps were estimated using equal thresholds for all sessions ($p = 0.05$; corrected for multiple comparisons). To express the effect of tactile coactivation on BOLD signal of contralateral SI and SII, we used the corresponding number of activated voxels per cluster which were included into following formula: $\boldsymbol{K} = ((\text{right}_{post} - \text{right}_{pre}) - (\text{left}_{post} - \text{left}_{pre}))/\text{right}_{pre}$.

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