

Effects of co-activation on cortical organization and discrimination performance

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We used fMRI to investigate the effects of tactile co-activation on the topographic organization of the human primary somatosensory cortex (SI). Behavioral consequences of co-activation were studied in a psychophysical task assessing the mislocalization of tactile stimuli. Co-activation was applied to the index, middle and ring fingers of the right hand either synchronously or asynchronously. Cortical representations for synchronously co-activated fingers moved closer together, whereas cortical representations

for asynchronously co-activated fingers became segregated. Behaviorally, this pattern coincided with an increased and reduced number of mislocalizations between synchronously and asynchronously co-activated fingers, respectively. Thus, both synchronous and asynchronous coupling of passive tactile stimulation is able to induce short-term cortical reorganization associated with functionally relevant changes. *NeuroReport* 15:2669–2672 © 2004 Lippincott Williams & Wilkins.

Key words: Cortical organization; fMRI; Psychophysics; Somatosensory cortex; Synchronous and asynchronous co-activation

INTRODUCTION

Protocols of paired tactile stimulation are effective in evoking cortical reorganization [1–4], indicating that Hebbian mechanisms play an important role in somatosensory cortical plasticity. According to Hebb, temporal and spatial coincidence of behaviorally relevant stimuli should drive neurons to respond to those stimuli in a temporally coherent manner, therefore providing the basis for cortical reorganization [5]. In rats, for example, paired stimulation of neighbored vibrissae or separated receptive fields on digits or pads resulted in an enlargement of the cortical areas representing the stimulated skin locations and an increase of their overlap [1–3].

Recently it has been shown in humans that protocols of synchronous tactile co-activation without attention directed to the stimuli are also sufficient to induce comparable reorganization in the primary somatosensory cortex (SI), paralleled by changes in tactile discrimination performance [6–10]. Reorganization due to passive synchronous co-activation is thereby comparable to reorganization after active training (for review see [11]), suggesting that both top-down and bottom-up mechanisms are involved in these processes.

Although many studies describe the role of synchronous co-activation for cortical plasticity, only little is known about consequences of asynchronous tactile co-activation either on cortical topography or on behavior. Therefore, we combined synchronous and asynchronous passive tactile stimulation of different fingers to investigate related changes in the ability to localize tactile stimuli and in the functional

organization of the human somatosensory cortex as measured with functional MRI. As far as we know this is the first study combining synchronous and asynchronous passive co-activation in a single experiment allowing to examine the exact role of input timing for cortical plasticity and related behavioral changes. Under control conditions, representations of the fingers show a strict topographic order with the thumb represented most inferiorly and the little finger most medially on the postcentral gyrus [12]. We expected an integration of the representations of synchronously co-activated fingers indicated by decreased distance between the activation maxima and a segregation of the representations of asynchronously co-activated fingers indicated by an increased distance between the activation maxima. We further hypothesized that these changes might be paralleled by increased numbers of mislocalizations between synchronously stimulated fingers, and less mislocalizations between asynchronously stimulated fingers.

MATERIALS AND METHODS

Fifteen healthy right-handed volunteers (six female, nine male, age 20–33 years) participated in this study after giving written informed consent. The study was approved by the local ethics committee and conducted in full accordance with the Declaration of Helsinki.

In order to study behavioral and functional consequences of tactile co-activation, synchronous and asynchronous stimulation of finger tips was applied to all subjects in a conditioning session lasting three hours. Subjects' percep-

tual performance in a tactile localization task was assessed one week prior to the conditioning session (pre-test), after conditioning (post-test) and in an additional session one week after conditioning to control for recovery (recovery). Using fMRI, the functional mapping of the cortical representations of index, middle and ring fingers of both left (control) and right hand took place directly after the conditioning session.

Co-activation was applied to index, middle and ring fingers of the right hand using three small electromagnetic solenoids with a diameter of 8 mm [2,8,9,13]. These solenoids were mounted to the distal phalanges of each finger and transmitted the tactile stimuli which were generated by applying a short electrical pulse to the solenoids. Pulses were recorded on tape and played back via a portable tape recorder during the conditioning session. Interstimulus intervals (ISIs) of the presented pulses varied randomly between 8 and 1761 ms with a mean repetition rate of 1.7 Hz. Two of the solenoids were fed with the output of one channel of the tape recorder leading to synchronous stimulation of these fingers. The other channel provided input for the remaining finger leading to asynchronous stimulation. The order of whether the index or ring finger was stimulated asynchronously, compared with the other two fingers being stimulated synchronously, was randomized across subjects. Stimuli were applied for three hours at supra-threshold intensities. During co-activation, subjects were asked not to attend to the stimulation and resumed their everyday routine.

The percentage of mislocalizations of light tactile stimuli across fingers was determined using von Frey hairs [14,15]. In an eight-alternative forced choice paradigm, stimulation was applied to two locations ~0.3 mm left and right of the center of the distal phalanges of each small, index, middle and ring fingers of the right hand and thus within range of the area being co-activated. The applied weights used were 280, 160, 100, 90, 70, 60, 50, 30, 20, 10, 7, 5 and 3 mg. Before each of the three sessions the localization threshold was determined for each finger separately. Threshold was defined as the weight at which subjects could correctly identify the stimulus location in >75% of the trials. One session consisted of 20 trials for each index, middle and ring finger and additional ten trials for the small finger. Although not co-activated, the small finger was included into the psychophysical testing, because we did not want to constrain subjects in their estimation of the stimulus location. The thumb was not included, because in a pilot experiment, subjects rarely mislocalized stimuli to the thumb. Trials were randomized across the four fingers. On each trial the tip of the von Frey hair was applied manually to the skin and pressure was exerted until the filament bent for ~1 s. Subjects had to respond as soon as possible on which of the eight locations they felt the stimulus. They were asked to keep their eyes closed during the testing period to prevent visual verification of the stimulation site. For each session the amount of mislocalizations between fingers being co-activated synchronously and asynchronously was calculated as the percentage of the total amount of mislocalizations for that session.

A 1.5T Siemens scanner was used for echo-planar imaging (EPI) of the cortical representation of index, middle and ring fingers of both left (control) and right hand (TR 3 s, TE 60 ms, matrix 64 × 64, voxel size 3 × 3 × 4 mm³, 28 slices). Additionally, a high-resolution T1-weighted anatomical 3D-

dataset was acquired. Pneumatically driven stimuli were applied to the distal phalanges of index, middle and ring fingers of both hands in a block design in two sessions for each hand (four sessions in total, 125 volumes per session, 5 volumes per block, 4 blocks of stimulation on index, middle and ring fingers alternating with blocks of no stimulation as baseline). One block consisted of 40 stimuli applied with randomly varying ISIs between 250 and 400 ms resulting in an average stimulation frequency of 3 Hz. Blocks were randomized across fingers of each hand per subject. Data were pre-processed and statistically analyzed using SPM99 (Wellcome Department of Imaging Neuroscience, London, UK). A general linear model (GLM) was applied to the time course of each voxel [16]. For all subjects the number of active voxels ($p < 0.001$) was determined for each finger with respect to the baseline for primary and secondary somatosensory cortices (SI and SII). The Euclidean distance was calculated between the three dimensional MNI coordinates of the local maxima of activation in SI and SII for the stimulated fingers. Distance measurements between adjacent fingers being co-activated synchronously or asynchronously were analyzed using non-parametric statistics (Wilcoxon signed rank test). Comparing both conditions (synchronous *vs* asynchronous co-activation) first within the same hemisphere and second against the representation of the left control hand a pre fMRI session was not necessary to validate the effects.

RESULTS

Psychophysics: Subjects made significantly fewer mislocalizations between fingers being stimulated asynchronously and significantly more mislocalizations between fingers being stimulated synchronously in the post-test as compared with the pre-test (Fig. 1). A repeated measures ANOVA with the factors session (pre-test, post-test, recovery) and condition (synchronous and asynchronous) yielded a significant session × condition interaction ($F(2,18)=6.011$, $p < 0.04$) with the number of mislocalizations in the post-test being significantly higher after synchronous than after asynchronous co-activation ($p < 0.005$). *Post-hoc t*-tests revealed that values of the pre- and post-test were significantly different for asynchronously stimulated fingers ($p < 0.05$) and roughly significantly different for synchronously stimulated fingers ($p = 0.06$). No significant differences could be found between the pre-test and the recovery for synchronous as well as for asynchronous co-activation,

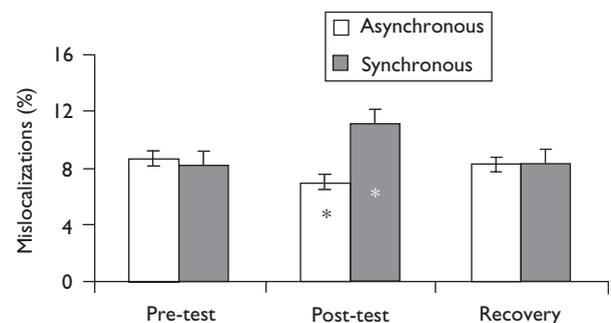


Fig. 1. Percentage of mislocalizations across synchronously and asynchronously co-activated fingers for pre-test, post-test and recovery (mean and s.e.m.; * $p < 0.06$).

indicating complete reversibility of the described effect within 1 week.

fMRI: Figure 2 shows the overall cortical activation patterns after tactile stimulation of the three middle fingers of both hands. fMRI revealed strong activations in the respective contralateral SI and SII, as well as in ipsilateral SII in some of the subjects. However, only topographic order in contralateral SI was significantly different for the experimental conditions (Fig. 3a). As expected, in the right control hemisphere the cortical activation maxima are clearly separated and arranged in strict topographic order with the representation of the index finger most inferiorly and the representation of the ring finger most superiorly. Topographic order in the left SI was very different. Activations for the synchronously activated fingers, in this case middle and ring finger, show a great overlap. In contrast, the representation of the index finger, which was stimulated asynchronously to the other fingers is clearly separated.

Figure 3b allows direct comparison of this example to another subject in which the ring finger was stimulated asynchronously. In this case, representations of the index

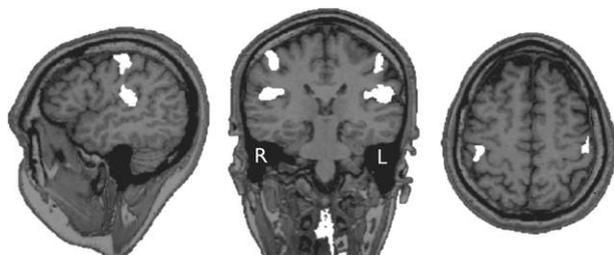


Fig. 2. Cortical activation after right and left hand finger stimulation. R/L: Right/left hemisphere. Activation maps for both hands are superimposed.

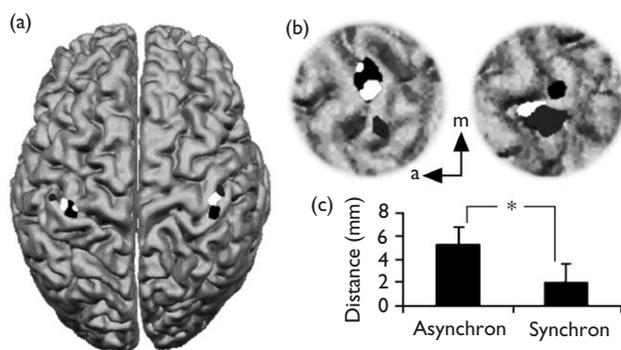


Fig. 3. (a) Cortical representations of the index (gray), middle (white) and ring (black) finger of the right and left hand. Representations within the left SI overlap for right middle and ring fingers that have been stimulated synchronously. The representation of the asynchronously stimulated index finger is located further apart. (b) Enlarged view on the postcentral gyrus of the left hemisphere (a, anterior, m, medial) from the example in (a) (left) and another subject where the ring finger was stimulated asynchronously (right). In both cases the representation of the asynchronously stimulated finger is well separated from the overlapping representations of the synchronously stimulated fingers. (c) Euclidean distance between synchronously and asynchronously co-activated fingers (mean and s.e.m.; * $p < 0.05$).

and middle finger are mostly overlapping and well separated from the ring finger representation.

Statistical analysis of individual results revealed a significant difference in the Euclidean distance between the local activation maxima for adjacent fingers being co-activated synchronously (mean distance=2.05 mm) compared with adjacent fingers being co-activated asynchronously (mean distance=5.24 mm, $Z = -2.032$, $p < 0.05$, Fig. 3c). For the left control hand, no difference could be observed in the Euclidean distance between the representations of the corresponding fingers (mean distance=3.42 mm, $p > 0.5$). Further, we found no effect for the number of active voxels, neither within the left (test) hemisphere nor between both hemispheres and no differences for the representations of the fingers of both left and right hand in SII.

DISCUSSION

Our results show that both asynchronous and synchronous co-activation leads to reorganization of the cortical representations of the co-activated fingers. Representations of synchronously co-activated fingers moved closer together, which was accompanied by more mislocalizations between these fingers. By comparison, representations of asynchronously co-activated fingers moved further apart, which coincided with fewer mislocalizations between those fingers.

These effects and their reversibility are well in line with recent electrophysiological recordings in rats [1–3], and fMRI, MEG and SEP mapping experiments in humans [7–10,13] which revealed consistent integrative effects of synchronous co-activation. Interestingly, synchronous co-activation improved human two-point discrimination performance [6–10,13], while frequency discrimination [10] and localization [17] became impaired.

Even long-term synchronous usage of fingers in monkeys during training in a tactile discrimination task resulted in an integration of the representations of those body parts that received temporally coincident inputs [18]. In humans, examination of the cortical hand representations of blind Braille readers, who use three fingers of each hand in synchrony for reading [19] revealed a distortion of the normal cortical topography due to an increase of overlap. Intensive daily musical practice leading to tactile input synchronicity is associated with a fusion of the cortical representations of the engaged fingers [20]. Simultaneous finger stimulation during a pattern discrimination task also yielded reduced distances between co-activated finger representations and increased mislocalizations [21].

On the cellular level, direction and magnitude of synaptic modification depends critically on the relative timing of the pre- and postsynaptic spikes beyond exact synchronicity [22]. At the level of cortical maps and behavior now our actual study extends earlier experiments to the role of asynchronicity of tactile inputs for the induction of cortical plasticity and behavioral changes.

Using asynchronous co-activation, Dinse *et al.* detected an impairment of 2-point discrimination, but an improvement of localization abilities on the stimulated skin sites [17]. While these findings indicate a trade-off between discrimination and localization (cf. [19]), our results confirm that differential perceptual consequences in a localization task depend on the direction of cortical integration and segregation processes. These processes, in turn, are due to the

degree of synchronicity in tactile co-activation. Importantly, control experiments consisting of a single-site stimulation using otherwise identical stimulation protocols of frequency and duration resulted consistently in a lack of changes on all levels described above [2,11], indicating that the aspect of co-activation is crucial for the induction of plastic changes.

Several conceptual and computational models have been put forward to explain the mechanisms underlying cortical map reorganization. The main hypothesis suggested in this context is based on the assumption that synaptic connections between neurons being activated in synchrony become stronger. Pearson *et al.* [23] and Grajski and Merzenich [24] suggested a model in which a Hebbian learning rule strengthens the connections between co-activated neurons, whereas a competitive mechanism helps to maintain the total amount of synaptic input to a cell. For example, if some synapses are strengthened due to co-activation, all other synapses will be decreased by a certain fraction. If synaptic connections between neurons are weakened on the other hand, all other connections are increased by a certain amount. According to this model by synchronous stimulation of two fingers, synaptic connections between their cortical representations are strengthened and their local activation maxima move closer together whereas in the case of asynchronous stimulation, synaptic connections are weakened and the activation maxima move further apart. In addition, the extended Hebbian learning model can also explain our findings concerning the perceptual changes accompanying reorganization. Due to the weakened synaptic connections between asynchronously activated neurons, neuronal activity in finger representations is rather focal and does not spread to more distant representational zones. Therefore, tactile stimuli applied to asynchronously stimulated fingers only activate the genuine representational zone of that finger and thus can be localized much easier. In contrast, synchronous stimulation of two fingers strengthens synaptic connections between the corresponding representational zones. Therefore, stimulating one of the two fingers that had been previously co-activated synchronously in a conditioning procedure, always activates both representational zones and the stimulus cannot be localized easily, leading to an increased frequency of mislocalizations between synchronously co-activated fingers.

CONCLUSION

Not only synchronous but also asynchronous co-activation is effective in inducing cortical reorganization accompanied by altered behavioral performance in tactile localization. This suggests that the timing of the tactile co-activation protocol plays a critical role in the direction of cortical changes and related behavioral consequences.

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