Facilitating Effect of 15-Hz Repetitive Transcranial Magnetic Stimulation on Tactile Perceptual Learning

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Abstract

■ Recent neuroimaging studies have revealed that tactile perceptual learning can lead to substantial reorganizational changes of the brain. We report here for the first time that combining high-frequency (15 Hz) repetitive transcranial magnetic stimulation (rTMS) over the primary somatosensory cortex (SI) with tactile discrimination training is capable of facilitating operant perceptual learning. Most notably, increasing the excitability of SI by 15-Hz rTMS improved perceptual learning in *spatial*, but not in *temporal*, discrimination tasks. These findings give causal support to recent correlative data obtained by functional magnetic resonance imaging studies indicating a differential role of SI in spatial and temporal discrimination learning. The introduced combination of rTMS and tactile discrimination training may provide new therapeutic potentials in facilitating neuropsychological rehabilitation of functional deficits after lesions of the somatosensory cortex. ■

INTRODUCTION

Training and learning can induce substantial reorganizational changes of the brain, which are referred to as use- or experience-dependent plasticity (Pantev et al., 1998; Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Pascual-Leone & Torres, 1993; Recanzone, Merzenich, Jenkins, Grajski, & Dinse, 1992). Recent neuroimaging studies have demonstrated a direct relationship between cortical plastic changes and improvement of psychophysically assessed performance (Hodzic, Karim, Veit, Erb, & Godde, 2004; Pleger et al., 2003; Sterr et al., 1998). Moreover, these findings have been shown to be of eminent clinical relevance because they are being currently used in the neuropsychological rehabilitation of brain lesions through different kinds of training protocols (Flor, Denke, Schaefer, & Grusser, 2001; Levin & Grafman, 2000; Cohen, Ziemann, & Chen, 1999; Hamdy, Rothwell, Aziz, Singh, & Thompson, 1998). However, to date, there are contradicting views concerning the topography of tactile learning in humans, for instance, how far do "early" and "late" cortical regions contribute to tactile information processing and how far are different types of tactile discrimination learning affected such as in *spatial* versus *temporal* discrimination tasks (Romo & Salinas, 2003; Gilbert, Sigman, & Crist, 2001; Harris, Harris, & Diamond, 2001). Complementary to previous correlative evidence for the role of the primary somatosensory cortex (SI) in tactile learning obtained by functional magnetic resonance imaging (fMRI) studies (Hodzic, et al., 2004; Pleger et al., 2003), direct "causal" evidence for the role of SI in different kinds of tactile perceptual learning can be revealed by transcranial magnetic stimulation (TMS), whereby the stimulated cortical area can be inhibited or facilitated, dependent on the applied stimulation protocol (Karim et al., 2003; Hallett, 2000). Several studies have shown that low-frequency repetitive TMS (rTMS) of 1 Hz or less is capable of inhibiting the excitability of the motor cortex (Muellbacher, Ziemann, Boroojerdi, & Hallett, 2000; Chen et al., 1997), whereas high-frequency rTMS (5 Hz and more) is known to facilitate the excitability of the stimulated motor cortex (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994). Similar effects of rTMS on cortical excitability have been shown for the visual and somatosensory cortex (Tegenthoff et al., 2005; Boorojerdi, Prager, Muellbacher, & Cohen, 2000). Although the majority of TMS studies in the last decade were concerned with the motor system, there is current interest in TMS studies on higher cognitive functions such as working memory (Harris, Miniussi, Harris, & Diamond, 2002; Grafman & Wassermann, 1999), language (Mottaghy et al., 1999), and visual functions (Hilgetag, Theoret, & Pascual-Leone, 2001). Nevertheless, to date, little is known about the effects of rTMS on learning processes (Grafman, 2002). Although Ragert et al. (2003) demonstrated that rTMS might facilitate improvements in
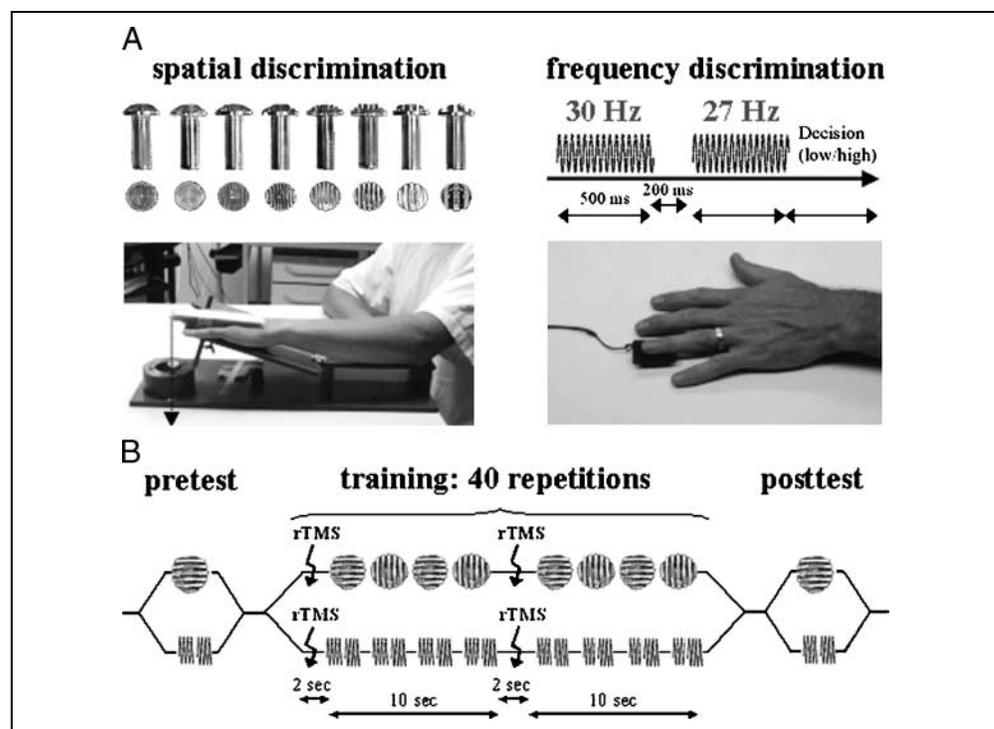
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spatial discrimination performance induced by extensive passive tactile stimulation, this article presents the first attempt to detect rTMS-induced effects on operant perceptual learning. Operant conditioning is a widely applied learning paradigm which states that if a particular stimulus–response (S–R) pattern is positively or negatively reinforced, the individual will be conditioned to show this behavioral pattern more or less frequently (Skinner, 1953). In line with this assumption, Herzog and Fahle (1998) have reported that perceptual discrimination learning is much more effective using external feedback (positive or negative reinforcement) than without feedback. Moreover, it has been shown that operant discrimination learning can lead to substantial functional reorganizational changes of the primary sensory cortex (SI) in animals (Jenkins, Merzenich, Ochs, Allard, & Guic-Robels, 1990) and in humans (Braun, Schweizer, Elbert, Birbaumer, & Taub, 2000). Thus, the aim of this study was to investigate: (a) whether enhancing the excitability of the primary sensory cortex (SI) by high-frequency rTMS would facilitate operant perceptual learning and (b) the specificity of this effect for different tasks such as in *spatial* and *temporal* discrimination.

Two kinds of tactile stimuli were applied. For testing spatial discrimination performance, we used a grating orientation task (GOT) in a two-alternative forced-choice paradigm (Van Boven & Johnson, 1994), where subjects were asked to report the orientation of the grating on the tip of their left ring finger. For testing temporal discrimination performance, two vibrotactile stimuli were applied on the same finger with different frequencies (frequency discrimination task, FDT). In a two-alternative forced-choice procedure, subjects were requested to judge if the frequency of the first stimulus was higher or lower than that of the second one. The experimental procedure consisted of three phases: (1) a pretest phase, in which spatial and frequency discrimination thresholds were psychophysically assessed without feedback; (2) a learning phase, in which we combined a feedback-driven, adaptive staircase training protocol for spatial and frequency discrimination on the left ring finger with 15-Hz rTMS over the right primary somatosensory cortex; and (3) a posttest phase to investigate the transfer effect from the training, again without feedback (cf. Figure 1). The performance of this experimental group was contrasted with one control group receiving the same test and training procedure but with sham rTMS as placebo control and a second control group receiving verum rTMS as the experimental group but without tactile discrimination training.

Figure 1. Methods. (A) Discrimination tasks. Two kinds of tactile discrimination tasks were applied. For testing spatial discrimination performance, we used gratings of different spacing, which orientation on the tip of the left ring finger had to be discriminated. For testing frequency discrimination performance, two vibrotactile stimuli were applied on the same finger with different frequencies. In a two-alternative forced–choice procedure, subjects were requested to judge whether the frequency of the first stimulus was higher or lower than that of the second one. (B) Experimental paradigm. GOT and FDT experiments were performed separately but immediately after each other in randomized order. They consisted of a psychophysical pretest of tactile discrimination thresholds, an operant training procedure to improve tactile discrimination performance, and a posttest. Training sessions were performed in a staircase procedure, which consisted of 40 blocks with eight trials each lasting 20 sec per block. Two trains of 15-Hz rTMS were applied in each block. Each single train lasted 2 sec with an intertrain interval of 10 sec. During this intertrain interval and immediately after each rTMS train, four trials of tactile discrimination were performed. Immediately before and after the training, the respective pretests and posttests were performed in series of ascending difficulties starting with the easiest stimulus (3.0 mm or 21 Hz) and ending when less then 75% correct responses occurred within a block of 20 test stimuli of the same grating width or frequency.

METHODS

Subjects

Thirty-six right-handed healthy subjects (23 men; aged between 18 and 38 years) participated in this study after giving written informed consent. The work was conducted in strict accordance with the local ethics policies. The experiments consisted of a psychophysical pretest of tactile discrimination abilities with the left ring finger, a training procedure to improve performance with this finger, and a posttest (cf. Figure 1B). Twenty-six subjects were trained in spatial and frequency discrimination at two separate sessions on the same day in randomized order. Sixteen subjects received 15 Hz rTMS during training. Ten subjects received sham rTMS as placebo control (Amedi, Floel, Knecht, Zohary, & Cohen, 2004; Lisanby, Gutman, Luber, Schroeder, & Sackeim, 2001). Because this control group received only sham rTMS and as all other subjects had not received verum TMS before, they were not able to compare differences in somatosensory sensations between the verum and the placebo condition, and thus, could not identify the sham rTMS as control condition. Ten subjects of a second control group received the same rTMS procedure as the experimental group but without combination with tactile discrimination training. Tactile tests were performed by assistants who were blind to the experimental hypotheses as were the subjects.

Tests of Spatial and Temporal Discrimination Performance

For testing spatial discrimination performance, we used a GOT in a two-alternative forced-choice paradigm (Van Boven & Johnson, 1994). The stimuli consisted of eight hemispherical plastic domes with gratings cut into their surfaces, resulting in parallel bars and grooves of equal width (JVP Domes, Stoelting, Wood Dale, IL, USA). The widths of the bars and grooves varied between domes from 0.25 and 3.0 mm. With the help of a custom-built apparatus, gratings were manually applied by the experimenter perpendicularly to the surface of the skin of the left ring fingertip for a duration of approximately 1.5 sec and indenting the skin by about 2 mm (cf. Figure 1A). The hand and fingers of the subjects were fixed to the platform of the apparatus so that no active touch could be applied to the probe by the subjects. The ridges and grooves were oriented parallel or orthogonal to the axis of the test finger in random order. Subjects were blindfolded and asked to report the orientation of the grating. Trials in which the subjects failed to respond immediately were rejected, as well as trials in which there were visible movements between skin and domes. Each dome was applied 20 times in one block. The test was performed with a series of descending dome widths starting with the largest grating (3 mm) and ending when the subject scored less then 75% correct re-

sponses within one block. The gratings discrimination threshold was defined as the level at which 75% of the responses were correct. Performance at this level is midway between chance and perfect performance and is a standard psychophysical criterion for thresholds determination (Van Boven & Johnson, 1994). In order to interpolate from the observed data the grating spacing that would have given a 75% correct response level, the following formula was used:

$$T_{G75} = G_{below} + \left(\frac{0.75 - P_{below}}{P_{above} - P_{below}} \right) \times (G_{above} - G_{below})$$

(1)

where T_{G75} = estimated threshold for the grating spacing on which the subject would have scored 75% had it been present; G = grating spacing; P = trials correct/N; N = number of trials; below = grating spacing or the probability of a correct response on the highest grating spacing on which the subject responded correctly *less* than 75% of the time; above = grating spacing or the probability of a correct response on the lowest grating spacing on which the subject responded correctly *better* than 75% of the time.

For temporal discrimination tests, vibrotactile stimuli were played back on micro-loudspeakers connected to a computer. The square-wave stimuli with constant amplitude applied to the fingertip by the solenoid of the loudspeaker lasted 500 msec and the interval between the two stimuli was 200 msec. In each trial, a reference frequency of 30 Hz and a test frequency between 21 and 30 Hz were presented in randomized order (cf. Figure 1A). Subjects had to decide within 500 msec, in two-alternative forced-choice manner, if the frequency of the first stimulus was higher or lower than that of the second one. As in the GOT, this FDT was performed in a series of ascending difficulties starting with the easiest stimulus (21 Hz) and ending when less than 75% correct responses occurred within a block of 20 test stimuli of the same frequency. The estimation of the frequency discrimination threshold was calculated analogical to the GOT using the following formula.

$$T_{F75} = F_{below} + \left(\frac{0.75 - P_{below}}{P_{above} - P_{below}} \right) \times (F_{above} - F_{below})$$

(2)

where T_{F75} = estimated threshold for the test frequency on which the subject would have scored 75% had it been present; F = test frequency; P = trials correct/N; N = number of trials; below = test frequency or the probability of a correct response on the lowest test frequency on which the subject responded correctly

less than 75% of the time; above = test frequency or the probability of a correct response on the highest test frequency on which the subject responded correctly *better* than 75% of the time.

No feedback was given during either discrimination tests.

Training Procedure

We applied an operant training protocol with auditory feedback (''correct'' vs. ''wrong'') in the GOT and in the FDT using an adaptive staircase procedure. During training, but not in the pretest and posttest, feedback was given after each single trial so that subjects were able to relate their errors to their perception in the respective trials and to improve perception. Tactile training consisted of 40 blocks with eight trials each (cf. Figure 1B). For the GOT, each subject began at the level that was one step more difficult than the subject's threshold level established by the pretest. The staircase procedure used an ascending series of stimulus difficulty levels until the subject made more than two mistakes within a block of eight trials. In this case, the direction of the staircase was reversed, decreasing the stimulus difficulty until six correct responses were reached within one block. Then the staircase direction was again reversed. The same procedure was used for training in the FDT with the exception that the first stimulus was a 21-Hz test stimulus. To avoid incidental learning during the pre- and posttests, feedback was restricted to the training phase and was given there after each single trial. As shown by Skinner (1953), this type of trial-by-trial feedback is very effective to positively and negatively reinforce correct and incorrect response patterns, respectively.

Application of rTMS

A Medtronic-Dantec Magnetic Stimulator (Skovlunde, Denmark) connected to a focal eight-shaped coil (MC-B70) was used for the TMS application. The procedure to define the stimulation intensity and to place the coil over the contralateral cortical finger representation was similar to those described by Ragert et al. (2003). At the beginning of each experimental session, the subject's resting motor thresholds (MT) were measured at the left abductor pollicis brevis muscle using single-pulse TMS. MT was defined as the lowest intensity capable of evoking 5 out of 10 motor-evoked potentials (MEPs) with peak-to-peak amplitudes of at least 50 μV. To position the coil over the representation of the left ring finger in the right SI cortex, the coil was moved in accordance with Maldjian, Gottschalk, Patel, Detre, and Alsop (1999) 1 to 2 cm posterior in parasagittal direction, where subjects reported the highest sensible sensations in their left ring finger induced by single-pulse

TMS (intensity 90% of the MT) such as tickling or prickling (Tegenthoff et al, 2005; Ragert et al., 2003). The subjects were asked to describe the intensity of the elicited sensations on an arbitrary scale of 1 to 5, with 5 being the strongest intensity. The point where the highest intensity was reported was determined as the optimal point. The location of the coil was marked and fixed at this position, and the intensity for rTMS during training was set at 90% of each individual's MT.

For sham stimulation, the magnetic coil was placed perpendicular to the skull surface so that little magnetic field could reach the underlying brain tissue (Lisanby et al., 2001).

During the training sessions, 80 trains of rTMS were applied in 40 blocks. Each single train consisted of 30 single pulses with a repetition rate of 15 Hz lasting 2 sec with an intertrain interval of 10 sec. During this inter-train interval, four trials of tactile discrimination were performed resulting in two TMS trains and eight discrimination trials per block. After each of these blocks, the grating width or frequency difference for the next block was adjusted according to the staircase protocol.

Data Analysis

Tactile discrimination performance was analyzed separately for the training period itself and for the pretraining and posttraining tests. To determine the overall performance during training, the differences (in mm for the gratings and in Hz for the frequencies) between the test and the start stimulus were calculated for each trial and were averaged for all trials together. This average difference was used as a measure of the performance during the training period. For the pre- and the posttests, thresholds T_{G75} (for the GOT) and T_{F75} (for the FDT) were calculated as described above. A repeated-measures ANOVA was performed for the variable ''performance,'' with experimental group (sham vs. TMS) as a fixed factor, and session (pre, training, post) as a repeated measure.

RESULTS

Spatial Discrimination

The results of the GOT training procedure are shown in Figure 2A. As expected, for both the TMS group and the sham control group, we found an improvement during training as indicated by a decrease of the gratings width for which orientation of the domes could be detected. A repeated-measures analysis of variance (ANOVA) with group (sham vs. TMS) as fixed factor and training block (with block 0 as the pretest) as repeated measure revealed no significant group difference [$F(1,17) = 0.64$, $p = .434$]. However, there was a significant block effect [$F(40,680) = 2.88$, $p < .0001$] indicating learning and a significant Block × Group interaction [$F(40,680) = 1.60$,
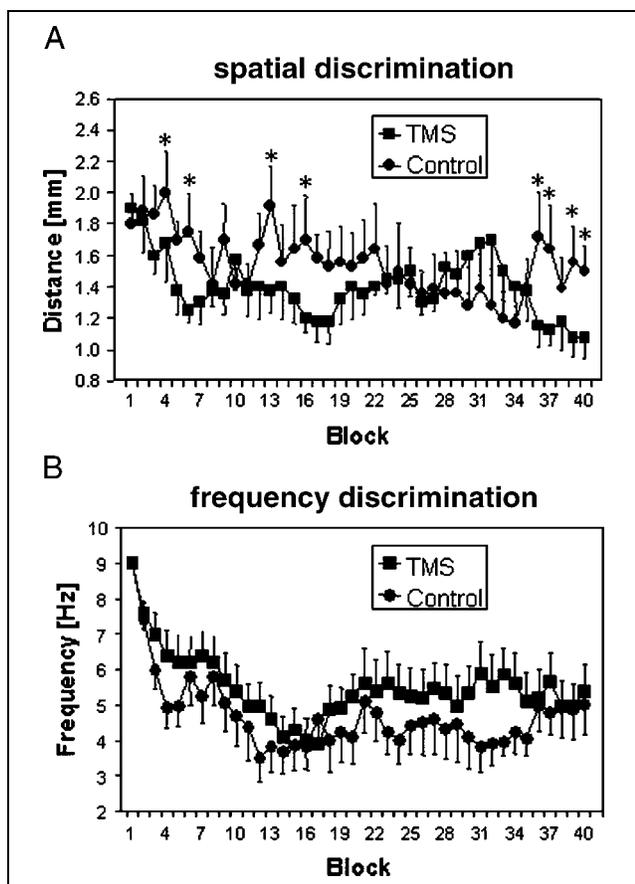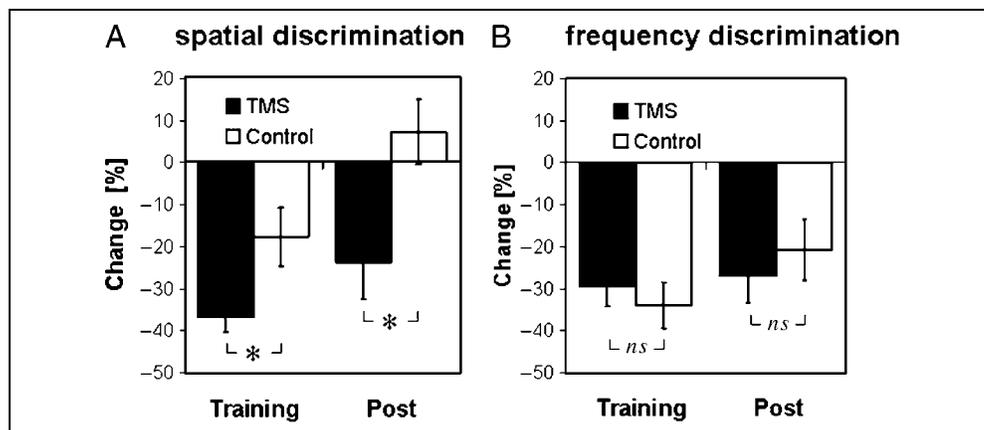
Figure 2. Learning curves. Improvement in performance during the 40 training blocks (filled circles: control group; filled squares: TMS group; mean and *SEM*). (A) During spatial discrimination training, both groups improved their discrimination performance with training. However, particularly during the last training blocks, subjects in the TMS group improved significantly stronger than the control subjects. *$p < .05$ in post hoc *t* tests for TMS versus control group. (B) Also during frequency discrimination training, both groups improved their discrimination performance with training. However, no differences between the groups were evident in this task.

$p = .012$], which was based on group differences in the following blocks as indicated by Bonferroni-corrected posthoc *t* tests ($p < .05$ for blocks 4, 6, 13, 16, 36, 37, 39, 40; cf. Figure 2A). Therefore, particularly during the last training blocks, subjects in the TMS group showed a stronger improvement than subjects in the control group. Moreover, there were also differences between the two groups in the posttest. Although the control group could not transfer the training effect to the posttest, the TMS group revealed a threshold level in the posttest that was significantly lower than in the pretest. For this analysis, we computed the relative improvement during training and the threshold changes in the posttest as compared to the pretest. Then an average value from the training blocks was used as a measure of change in the performance for the training period. As shown in Figure 3A, for both groups, performance during training improved by about −18% and −37% (control and TMS group, respectively). For the TMS group, this value remained negative (−23%) in the posttest, indicating a lasting training effect. For the control group, however, this value turned into positive values (+7%), revealing no significant change as compared to the pretest. Post hoc *t* tests confirmed that for the TMS group the threshold change in the posttest was significantly different from the pretest ($p = .018$) and from the control group's posttest ($p = .002$), whereas for the control group there was no difference between the pretest and the posttest ($p = .351$).

Frequency Discrimination

In the FDT, no differences were detectable between the TMS group and the control group during training as well as in the posttest. Similar to the GOT, in the FDT there was a strong improvement in discrimination during training indicated by a decrease in frequency differences, which could be discriminated (cf. Figure 2B). A

Figure 3. Training and transfer effects. Percent change in discrimination performance during training and in the posttraining session relative to the pretraining session (mean and *SEM*). (A) In the spatial discrimination task, the training effect was stronger for the TMS group than for the control group and only the TMS group remained better in the posttraining session as compared to the pretest. (B) In the frequency discrimination task, there was no difference between the groups. *$p < .05$ in post hoc *t* tests for TMS versus control group.

repeated-measures ANOVA revealed a significant block effect [$F(40,720) = 7.72, p < .0001$] but no group effect [$F(1,18) = 1.10, p = .31$] and no Group × Block interaction [$F(40,720) = 0.60, p = .98$]. Figure 3B illustrates the performance changes relative to the pre-test. During training discrimination performance improved by −34% and −29% [sham and TMS groups, respectively; significant session effect: $F(2,36) = 28.74, p < .0001$; posthoc t tests: $p < .0001$ for both groups]. In the posttest, for both groups, the learning effect persisted on a lower level, indicated by a threshold difference to the pretest of −21% and −27% (sham and TMS groups, respectively; $p < .002$ for both groups). In the training session and in the posttest, there was no significant difference between the two groups ($p = .47$ and $p = .31$, training and posttest, respectively).

In order to verify the facilitating effect of rTMS on operant learning and to investigate whether the combination of operant perceptual learning with high-frequency rTMS is in fact more effective than high-frequency rTMS alone, we conducted a further control experiment in which we tested another group of 10 subjects before and after the application of the same TMS protocol as in the experimental group, but without tactile discrimination training. As depicted in Figure 4, on average, we found a change in discrimination thresholds of −8.4% for frequency discrimination and −11.0% for spatial discrimination. These changes, however, were not significant (one-sided paired t test, $p > .09$ for both tasks).

DISCUSSION

Our data demonstrate that combining a tactile discrimination training protocol with high-frequency rTMS, the latter being well known to facilitate sensory and motor cortical excitability (Tegenthoff et al., 2005; Boorojerdi,
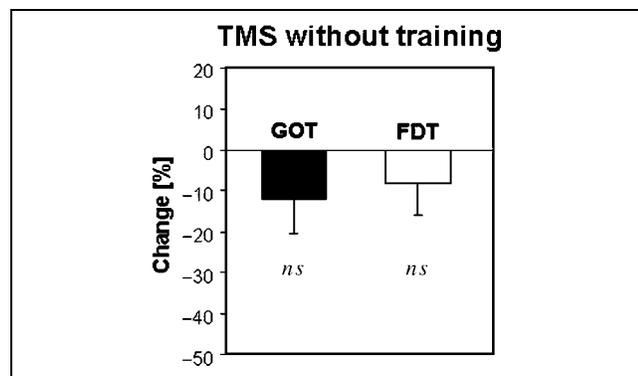

Figure 4. Effects of high-frequency rTMS without tactile discrimination training. Percent change of tactile discrimination performance in the spatial and in the frequency discrimination task after 15-Hz high-frequency rTMS over SI. The stimulation protocol was the same as in the experimental group except that the subjects did not receive operant discrimination training.

et al., 2000; Pascual-Leone, et al., 1994), is capable of facilitating operant perceptual learning. Most notably, we observed that high-frequency (15 Hz) rTMS over the contralateral primary sensory cortex (SI) improved spatial discrimination learning but had no effect on frequency discrimination learning. These findings support a recent fMRI study conducted in our group (Hodzic, et al., 2004), in which SI cortical reorganization in humans was strongly correlated to changes in spatial, but not temporal, discrimination abilities. This suggests that brain areas outside SI might be predominantly or more importantly involved in temporal tactile discrimination.

However, it remains unclear which representations—phase-locked activity in SI or frequency-correlated rate codes in SII—are the basis of perception and discrimination of vibration frequencies. Several studies provide contradicting views on this issue.

In monkeys, long-term frequency discrimination training altered cortical maps and receptive field properties in area 3b (SI) of monkeys (Recanzone et al., 1992). Psychophysical experiments in humans by Harris, et al. (2001) and Diamond, Petersen, and Harris (1999) revealed that performance of subjects in frequency discrimination depended on the topography of the cortical representations. Because somatotopic maps can be found in SI but not in SII (Merzenich, Kaas, Sur, & Lin, 1978), there seems to be strong evidence that activity in SI plays a major role in frequency discrimination.

Contrasting evidence has been provided by other studies. For instance, the group of Romo & Salinas (2001, 2003) studied neuronal activity in the cortex of monkeys during discrimination of different tactile vibratory stimuli. Using regular (periodic) and irregular (noisy) vibrations, they showed that in monkeys, activity in SII is best correlated to the discrimination performance. Imai et al. (2003) have demonstrated that in humans intensive training of tactile frequency discrimination led to a persistent improvement with the trained and neighboring finger but did not change the primary somatosensory cortical representation as measured with magnetic source imaging, whereas Braun et al. (2000) could intriguingly demonstrate that spatial discrimination training led to a differential functional reorganization in SI depending on the difference in the discrimination task.

Most recently, using fMRI, Pastor, Day, Macaluso, Friston, and Frackowiak (2004) found that in humans temporal and spatial discrimination tasks activate several common cortical areas, specifically the prefrontal cortex, the contralateral postcentral gyrus (the sensorimotor cortex), the inferior parietal lobule, the basal ganglia, and the cerebellum. However, there was activation in the presupplemental motor area and the anterior cingulate gyrus that was specific to the FDT, suggesting a particular role of these frontal areas in temporal processing.

Intriguingly, it has been shown that *inhibiting* or *disturbing* the activation of the primary sensory cortex (SI) by low-frequency rTMS (Knecht, Ellger, Breitenstein,

Ringelstein, & Henningsen, 2003), by cathodal transcranial direct current stimulation (tDCS) (Rogalewski, Breitenstein, Nitsche, Paulus, & Knecht, 2004), or by single-pulse TMS (Harris, et al., 2002) led to an impairment of frequency discrimination performance, but in contrast, *enhancing* the excitability of SI by anodal tDCS (Rogalewski, et al., 2004) or by high-frequency rTMS in combination with operant discrimination training, as shown in this study, did not lead to an improvement of frequency discrimination performance. These data suggest that information processing in FDTs passes the primary sensory cortex (SI) in an early stage, in which perceptual performance can be impaired by disturbing the activation of SI, but for acquisition and consolidation of frequency discrimination learning, other cortical areas seem to be predominantly or more importantly involved (cf. Pastor, et al., 2004).

One might suspect that rTMS-induced cortical activation was not restricted to the SI cortex but also involved the more anterior motor cortex or the more parietal cortical areas. Moreover, TMS over SI may have acted transsynaptically on other cortical sites, in turn responsible for learning effects. However, recent studies revealed that effects of TMS on tactile perception are very specific to the fingers whose representations are lying directly under the stimulation coil and cannot be transferred to other fingers on the same or opposite hand (Ragert et al., 2003; Harris, et al., 2002). Thus, although spreading activation beyond SI cannot be totally excluded in our experiments, these results strongly suggest a focal effect of rTMS as applied in this study. Furthermore, one might argue that using MR-guided TMS would have offered a higher precision in targeting SI. MRI-based neuronavigation can offer accurate positioning of the TMS coil over a specific cortical site, especially when there is no clearly defined TMS-induced output (e.g., MEPs, phosphenes, scotomas, sensory percepts) available as it is the case for most cognitive functions. However, if a direct response can be elicited by TMS, several studies have convincingly shown that positioning the TMS coil over the location that produces the maximal response (TMS activation maxima) is capable of modulating the cortical excitability of this region. These effects have been shown for the motor cortex (Chen et al., 1997; Pascual-Leone, et al., 1994), the visual cortex (Boorojerdi, et al., 2000), and the somatosensory cortex (Tegenthoff et al., 2005). Moreover, we have previously shown in the primary motor cortex that TMS and fMRI activation maxima are not identical (Lotze et al., 2003; Lotze et al., 2000). Thus, future research will have to (a) clarify the anatomical and functional relationship between TMS and fMRI activation maxima and (b) investigate if positioning the TMS coil over the fMRI activation maxima is more effective in modulating cortical excitability (as measured by MEPs, phosphene thresholds or tactile discrimination thresholds) than stimulating over the TMS activation maxima.

Dinse and colleagues demonstrated that 5 Hz rTMS alone over the contralateral hand representation is sufficient to improve tactile two-point discrimination, however, the combination of TMS and passive tactile coactivation was much more effective (Ragert et al., 2003; Ragert, Pleger, Tegenthoff, & Dinse, 2002). Thus, one might argue that in our experiment improved performance in the grating discrimination task was due to rTMS alone. In order to verify the facilitating effect of rTMS on operant learning and to investigate if the combination of operant perceptual learning with high-frequency rTMS is in fact more effective than high-frequency rTMS alone, we tested another group of 10 subjects before and after the application of the same TMS protocol as in the experimental group but without tactile discrimination training. For this group, we found, on average, a change in discrimination threshold of 8.4% for frequency discrimination and 11.0% for spatial discrimination; however, the changes were not significant and were far below the effects shown in the experimental group. This provides strong evidence that, indeed, the combination of rTMS with tactile discrimination training was the basis for the effects shown in our study and not high-frequency rTMS alone. Nevertheless, an increased sensitivity of the somatosensory cortex, due to rTMS as shown by Tegenthoff et al. (2005), might be an important factor for facilitation of learning as shown here.

Based on animal data, rTMS has been reported to induce long-term potentiation (LTP)-like or long-term depression (LTD)-like mechanisms depending on the stimulation frequency used, which can induce persistent effects on N-methyl-D-aspartate (NMDA) binding sites (Kole, Fuchs, Ziemann, Paulus, & Ebert, 1999). Ziemann, Hallett, and Cohen (1998) provided evidence that during ischemic nerve block, low-frequency rTMS application in humans also includes NMDA-receptor activation known to be involved in LTP-like processes. Using an NMDA antagonist, Dinse, Ragert, Pleger, Schwenkreis, and Tegenthoff (2003) have demonstrated that coactivation-induced perceptual learning and cortical reorganization can be completely blocked, indicating that NMDA-receptor activation is required for the manifestation of coactivation-induced perceptual learning. Moreover, there is convincing evidence that manipulating cortical excitability externally can improve learning processes. So far it has been demonstrated in neuropharmacological investigations that excitability-enhancing pharmacological agents, such as amphetamine, improve use-dependent plasticity (Bütefisch et al., 2002), whereas γ-aminobutyric acid agonists diminish it (Blin et al., 2001). Nitsche et al. (2003) have demonstrated that enhancing the cortical excitability of the primary motor cortex by anodal tDCS improves implicit motor learning. The acquisition of new skills is accompanied by changes of neural activity and excitability, which might reflect changes in synaptic strength as in NMDA receptor-dependent LTP, which has been shown

to be an important correlate of motor learning in the animal in vivo (Rioult-Pedotti, Friedman, & Donoghue, 2000).

Based on these results and that, dependent on the frequency of rTMS, LTP-like or LTD-like mechanisms can be induced (Hallett, 2000; Chen et al., 1997; Wang, Wang, & Scheich, 1996), we suggest a gating effect of 15 Hz rTMS in the training experiments reported here. This gating effect could enable stronger and more persistent learning in subjects of the TMS group under conditions which are not sufficient for lasting effects in the subjects of the control group.

To our knowledge, this is the first study to show that operant learning can be facilitated by rTMS. The introduced combination of rTMS and tactile discrimination training may also provide new therapeutical potentials for improving the rehabilitation of sensory functional deficits after lesions of the somatosensory cortex or in dystonic patients in comparison to the conventional operant training protocols currently used within the framework of neuropsychological rehabilitation. Therefore, further studies are necessary both to clarify the relationship between the rTMS dosing parameters and the duration of the after-effects and to investigate possible pharmacological acceleration of the rTMS-induced LTP-like effects.

Acknowledgments

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