Brain Stimulation (2011) ■, ■–■

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BRAIN STIMULATION

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Perceptual improvement following repetitive sensory stimulation depends monotonically on stimulation intensity

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Background
Electrical repetitive sensory stimulation (rSS) is a direct and effective means of inducing plasticity processes in human beings, and is increasingly being used as a therapeutic intervention. Suprathreshold intensities induce beneficial effects on tactile perception and sensorimotor abilities. However, it is not known whether there is an optimal range of stimulus intensity.

Methods
We investigated the effect of varied intensities (low, 1.19 ± 0.07 mA; intermediate, 3.33 ± 0.27 mA; and high, 4.42 ± 0.56 mA) on the outcome of a 30-minute electrical rSS applied to the index finger (intermittent high-frequency stimulation, 20 Hz and interburst interval, 5 seconds) in three groups (n = 10 each) of participants. As a marker of perceptual changes, we measured tactile spatial two-point discrimination on the stimulated finger and on the heel of the hand before and after the rSS.

Results
rSS improved discrimination performance, with the gain being the highest in the high-intensity group and the lowest in the low-intensity group. Measurements on the heel of the hand revealed small improvements in the high-intensity group, indicative of recruitment processes.

Conclusions
rSS of maximal intensity induced the strongest effects, indicative of a monotonic intensity-gain characteristic with no U-shaped dependency.

Keywords somatosensory cortex; plasticity; intervention; stroke rehabilitation

It is known that in addition to training, practice, and experience, perceptual performance can be improved by exposure to passive repetitive stimulation over a period of a few hours or less. Several forms of repetitive sensory stimulation (rSS) procedures involving techniques such as peripheral nerve stimulation,[1] somatosensory stimulation,[2]

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Submitted March 16, 2011; revised June 15, 2011. Accepted for publication July 5, 2011.

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doi:10.1016/j.brs.2011.07.002

exposure-based learning,[3,4] coactivation,[5-8] unattended activation-based learning,[9] and repetitive sensory stimulation[10,11] have been widely investigated as a means to drive learning as well as plasticity processes. There is accumulating evidence that these procedures might be useful in supplementing, enhancing, or even replacing training-based rehabilitation in the intervention of impaired populations such as stroke patients.[1,2,11]

Although many studies have shown that suprathreshold intensities are effective in driving perceptual and cortical changes, it is not known whether there is an optimal range of stimulus intensity. We therefore examined the effects of different intensities of rSS on tactile spatial two-point discrimination performance, which has been repeatedly shown to improve after rSS.

Methods

Thirty, healthy, right-handed[12] subjects (17 women and 13 men) aged 20-30 years (24.07 [2.72], mean [SD]) were tested in a tactile spatial two-point discrimination task. Subjects were randomly allocated to three experimental groups ($n = 10$ each) in which different stimulus intensities of electrical rSS were applied (low intensity, 1.19 ± 0.07 mA; medium intensity, 3.33 ± 0.27 mA; and high intensity, 4.42 ± 0.56 mA). The protocol was approved by the local ethics committee of Ruhr-University, Bochum. The project protocol was designed in accordance with the Declaration of Helsinki.

Two-point discrimination

Tactile two-point discrimination thresholds were assessed using the method of constant stimuli.[5-8] For a reliable assessment of spatial discrimination thresholds on the tip of the index finger, we used a custom-made apparatus that allowed a standardized form of testing.[9] In brief, seven pairs of rounded needle probes (diameter, 200 μm) with separation distances between 0.7 and 2.5 mm in 0.3 mm steps were used. For control, zero distance was tested with only a single needle probe. This procedure has been shown to provide high test-retest reliability (> 0.90; see Results[10]).

For the assessment of discrimination thresholds on the right heel of the hand, we used a hand-held device that allowed application of different separation distances with a constant force via calibrated springs (30 g). To account for interindividual differences in the tactile acuity of this portion of the hand, we used different sets of needle separations ranging from 3 to 10, 4 to 13, 7 to 14.5, and 8.5 to 20 mm. The appropriate set of needles was selected during pretesting. Skin indentations were approximately 0.5 to 1 mm.

For both skin sites, each distance including zero distance was presented seven times in randomized order resulting in 56 single trials per session. Subjects were aware that there were single needle probes presented, but they were unaware of its frequency of use. Subjects had to decide immediately if they had the sensation of one or two tips by answering "1" or "2." The summed responses were plotted against tip distance as a psychometric function and were fitted with a logistic regression model. Discrimination thresholds were taken at the point at which 50% correct responses (i.e., two tips perceived) were reached. To demonstrate that the changes in thresholds were unlikely to be due to changes in the response criterion, we used the false alarm as well as the hit rates to calculate a discrimination index (d' value).[7,13] For numerical calculation in case of zero false alarm rates, the false alarm rate was set at 0.125.

Stimulation protocol and adjustment of stimulation intensities

For electrical rSS, we used an intermittent high-frequency protocol of stimulation consisting of trains of 20 single pulses of 20 Hz for 1 second with an intertrain interval of 5 seconds.[14] The duration of application was 30 minutes, resulting in a total number of 6000 pulses. For application of the rSS, we used self-adhesive electrodes (1 × 4 cm), which were taped to the first (cathode) and third phalanx (anode) of the right index finger. Electrical pulses were delivered via a Neuropack S1 MEB-9400 series.

For each participant, intensity was adjusted in 0.1 mA steps in five subsequent trials. For stimulation in the low-intensity group (low rSS, 1.19 ± 0.07 mA), intensity was set to 0.1 mA above individual average sensory threshold. In the medium-intensity group (medium rSS, 3.33 ± 0.27 mA), intensity was set to the average value of the minimal intensity required to induce a sensation and the maximal individual intensity that could be tolerated without pain. In the high-intensity group (high rSS, 4.42 ± 0.56 mA), intensity was set to the maximal intensity tolerated without pain minus 0.1 mA.

Experiment schedule

Before rSS, discrimination thresholds were tested in three sessions (s1, s2, and s3) to obtain a stable baseline. Testing in each session lasted for approximately 5 minutes, and was separated by a few minutes. Previous studies had shown that initial task familiarization generalizes to other skin sites.[5-8] Therefore, the heel of the hand was only tested once before the rSS. Thresholds derived during s3 were used for further analysis (precondition). Reassessment of tactile performance was repeated approximately 10 minutes after termination of rSS in session four (postcondition).

Data analysis

Psychophysical data were statistically analyzed using repeated measures analysis of variance (rmANOVA) with

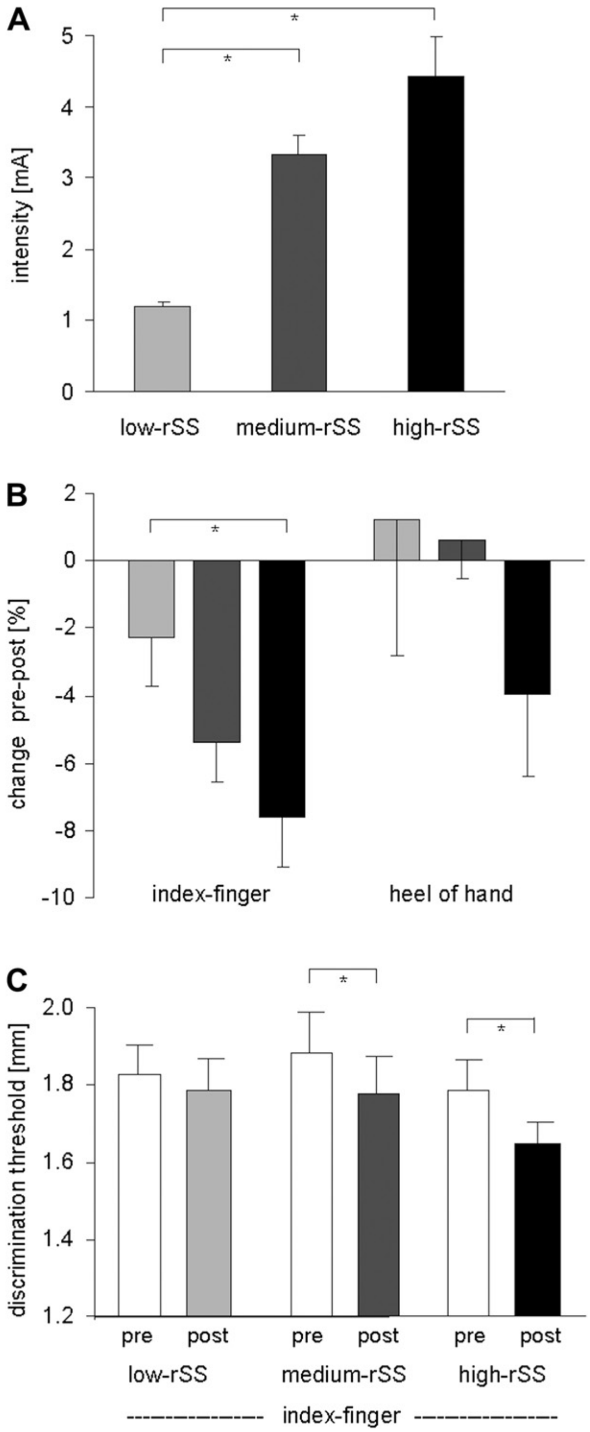

Figure 1 **A,** Average stimulation intensities (± SEM) used in the three experimental groups. Asterisks show significant differences between groups. **B,** Average changes in discrimination thresholds post versus pre (%) (± SEM) in the three groups. Left: discrimination changes in the stimulated index finger; right: discrimination changes in the nonstimulated heel of the hand. Asterisks show significant group differences. **C,** Average discrimination thresholds (± SEM) on the stimulated index finger before (pre) and after (post) application of the rSS in the three groups.

SESSION as a factor with post hoc analysis corrected for multiple comparisons (Bonferroni), and correlation analysis (Pearson correlation coefficient). All data were normally distributed as evaluated by Kolmogorov-Smirnov tests. Group data are expressed as mean ± (standard error of mean, SEM).

Results

Stimulation intensity

Average intensities were 1.19 ± 0.07 mA in the low-intensity, 3.33 ± 0.27 mA in the medium-intensity, and 4.42 ± 0.56 mA in the high-intensity groups (Figure 1A; n = 10 each), with significant differences between low rSS versus medium rSS and low rSS versus high rSS (Bonferroni post hoc test, $P \leq 0.001$).

Effect of different intensities on stimulation-induced gain of tactile discrimination

During s1, s2, and s3, all subjects achieved a stable baseline of discrimination performance as estimated by rmANOVA using SESSION as a factor ($F_{(2.58)} = 1.258$ and $P = 0.292$, n = 30). Analysis of Cronbach's alpha confirmed high test-retest reliability (s1 versus s2, 0.934 and s2 versus pre, 0.946).

After 30 minutes of rSS, increasing stimulation intensities resulted in progressively lower tactile discrimination thresholds (Pearson correlation $r = -0.384$ and $P = 0.036$, n = 30). After low rSS, discrimination thresholds were slightly reduced, resulting in an average improvement of −2.29 ± 1.44% (rmANOVA pre versus post: $F_{(1.9)} = 2.297$ and $P = 0.164$). In contrast, medium rSS resulted in a significant decrease in tactile discrimination thresholds of −5.36% (pre versus post: $F_{(1.9)} = 18.249$ and $P = 0.002$). After high rSS, discrimination thresholds showed the largest improvement of −7.61 ± 1.46% (pre versus post: $F_{(1.9)} = 21.418$ and $P = 0.001$; Figure 1B and C; for individual psychometric curves, Figure 2), which was significantly greater than that seen after low rSS (Bonferroni post hoc test, $P = 0.035$). Furthermore, there was an increase in the d′ value from 1.21 (0.18) (mean [SD]) to 1.37 (0.19) (pre versus post: $F_{(1.9)} = 17.527$ and $P = 0.002$) after high rSS. However, there was no significant increase in d′ following low (pre, 1.20 [0.25] and post, 1.27 [0.27]) and medium rSS (pre, 1.25 [0.11] and post, 1.31 [0.17]).

In addition to the stimulated index finger, we tested the right heel of the hand in all subjects to test for possible transfer of the rSS effects to other skin sites. Generally, discrimination thresholds and interindividual differences of thresholds were much higher on the heel of the hand as compared with the index finger. There were no significant effects on the discrimination abilities of the heel of the

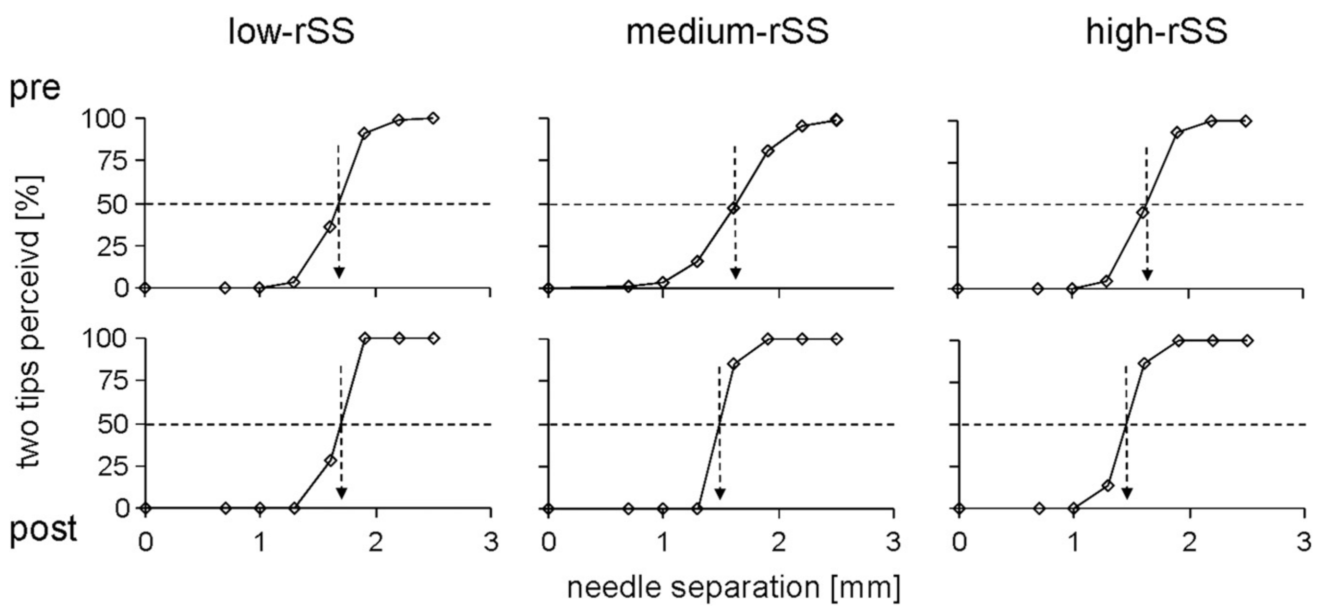

Figure 2 Psychometric curves illustrating the rSS-induced changes in discrimination thresholds of the stimulated index finger for one individual from each experimental group. Correct responses in percentages are plotted as a function of the separation distance as a logistic regression line (open diamonds). The 50% level of correct responses as well as resulting thresholds (arrows) are shown. (top): precondition (before rSS); (bottom): postcondition (after rSS).

hand after rSS applied to the index finger (rmANOVA pre versus post: low rSS, $F_{(1.9)} = 0.007$ and $P = 0.937$; medium rSS, $F_{(1.9)} = 0.186$ and $P = 0.677$; and high rSS, $F_{(1.9)} = 2.175$ and $P = 0.174$; Figure 1B). The d′ values were not affected in any of the groups.

Discussion

Electrical rSS applied to the finger has been repeatedly shown to improve tactile spatial discrimination abilities.[5-11] We found that stimulation with the maximal tolerable intensity resulted in the largest improvements in tactile spatial discrimination, whereas stimulation with an intensity that was weakly above the sensory threshold led to the smallest improvements, indicating that the effects of repetitive stimulation depend monotonically on intensity.

Single fiber and single neuron recordings have shown that intensity variations of cutaneous stimulation are transmitted in a fairly linear fashion to the somatosensory cortex.[15,16] Recording of somatosensory evoked magnetic fields to electric stimulation of the left median nerve using weak, medium, or strong stimuli revealed that the amplitude of the 20-millisecond response from the primary somatosensory cortex followed the stimulus intensity linearly, whereas signals from the second somatosensory and posterior parietal cortex were saturated at medium intensity.[17]

On the other hand, in an early study about long-term potentiation (LTP) induction in rat visual cortex, low-intensity tetanus was found to be more effective in producing LTP than is high-intensity tetanus, implicating an inverted-U relationship between intensity and LTP magnitude.[18] However, data on the intensity dependence of protocols for tetanic stimulation, LTP, and long-term depression are scarce. Plasticity mechanisms mediated by the rSS effects may be responsible for potential U-shaped dose-response characteristics.

Our data showed no evidence of saturation at high intensities. In fact, the largest benefit was observed in cases that received the rSS at maximal stimulation intensity. This monotonic dependency may be attributable to a greater number of nerve fibers being recruited at higher intensities, thus contributing to a progressively larger effect. The small, yet not-significant improvement in discrimination seen at the heel of the hand supports this assumption. Animal studies have shown that changes in the receptive fields of the digits tend to expand along the proximal-distal axis more easily than it does across fingers. To conclude, our results suggest the use of high-stimulation intensities in applications where maximal effects are desired, as in the case of intervention studies.

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