Homeostatic Metaplasticity in the Human Somatosensory Cortex

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Abstract

■ Long-term potentiation (LTP) and long-term depression (LTD) are regulated by homeostatic control mechanisms to maintain synaptic strength in a physiological range. Although homeostatic metaplasticity has been demonstrated in the human motor cortex, little is known to which extent it operates in other cortical areas and how it links to behavior. Here we tested homeostatic interactions between two stimulation protocols—paired associative stimulation (PAS) followed by peripheral high-frequency stimulation (pHFS)—on excitability in the human somatosensory cortex and tactile spatial discrimination threshold. PAS employed repeated pairs of electrical stimulation of the right median nerve followed by focal transcranial magnetic stimulation of the left somatosensory cortex at an interstimulus interval of the individual N20 latency minus 15 msec or N20 minus 2.5 msec to induce LTD- or LTP-like plasticity, respectively [Wolters, A., Schmidt, A., Schramm, A., Zeller, D., Naumann, M., Kunesch, E., et al. Timing-dependent plasticity in human primary somatosensory cortex. *Journal of Physiology, 565,* 1039–1052, 2005]. pHFS always consisted of 20-Hz trains of electrical stimulation of the right median nerve. Excitability in the somatosensory cortex was assessed by median nerve somatosensory evoked cortical potential amplitudes. Tactile spatial discrimination was tested by the grating orientation task. PAS had no significant effect on excitability in the somatosensory cortex or on tactile discrimination. However, the direction of effects induced by subsequent pHFS varied with the preconditioning PAS protocol: After PAS_{N20-15}, excitability tended to increase and tactile spatial discrimination threshold decreased. After $PAS_{N20-2.5}$, excitability decreased and discrimination threshold tended to increase. These interactions demonstrate that homeostatic metaplasticity operates in the human somatosensory cortex, controlling both cortical excitability and somatosensory skill. ■

INTRODUCTION

Central to the function of the cerebral cortex is its ability of changing its response to a given stimulus. The cerebral cortex exhibits substantial plasticity during development (Katz & Shatz, 1996) and the adult cortex maintains the capacity to plastic change: visual, auditory, somatosensory, and motor cortical maps can all reorganize (Cooke & Bliss, 2006; Buonomano & Merzenich, 1998). Noninvasive stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), paired associative stimulation (PAS), transcranial direct current stimulation, peripheral nerve stimulation or peripheral tactile stimulation, allow to study mechanisms of cortical plasticity in humans (Ziemann, 2004; Classen & Ziemann, 2003; Paulus, 2003; Pleger et al., 2001). For example, PAS can induce long-lasting bidirectional changes in excitability in the human primary motor cortex and in the somatosensory cortex depending on the interval between a pair of associative stimuli (Litvak et al., 2007; Müller, Orekhov, Liu, & Ziemann, 2007; Wolters et al., 2003, 2005; Ziemann, Ilic, Pauli, Meintzschel, & Ruge, 2004; Stefan, Kunesch, Cohen, Benecke, & Classen, 2000). These aftereffects are referred to as long-term potentiation (LTP)-like and long-term depression (LTD)-like plasticity as they resemble spike-timing dependent LTP and LTD of neuronal synapses (Cooke & Bliss, 2006). Stimulation-induced changes in excitability of somatosensory cortex are accompanied by behavioral changes in tactile discrimination tasks (Litvak et al., 2007; Pleger et al., 2006; Tegenthoff et al., 2005, 2006; Knecht, Ellger, Breitenstein, Bernd Ringelstein, & Henningsen, 2003).

Homeostatic metaplasticity enables both selective modification and maintenance of synaptic strength in a physiological range (Abbott & Nelson, 2000; Abraham & Tate, 1997). The Bienenstock–Cooper–Munro (BCM) theory of bidirectional synaptic plasticity provides a conceptual basis of homeostatic metaplasticity (Bienenstock, Cooper, & Munro, 1982). Fundamental to this model is the idea that neuronal activity is stabilized by dynamic adaptation of the synaptic modification threshold, postsynaptic activity above which induces LTP (Bienenstock et al., 1982). For example, prolonged postsynaptic activity would systematically increase the modification threshold and, consequently, favor the induction of LTD over LTP. In the

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hippocampus, a priming stimulation preceding high-frequency stimulation inhibits the induction of LTP, hereby confirming the BCM rule (Gisabella, Rowan, & Anwyl, 2003; Huang, Colino, Selig, & Malenka, 1992). In humans, homeostatic metaplasticity has recently been demonstrated in the primary motor cortex by studying the interactions between effects on motor cortical excitability induced by two subsequent transcranial stimulation protocols (Müller et al., 2007; Siebner et al., 2004; Iyer, Schleper, & Wassermann, 2003). However, it is unknown whether homeostatic metaplasticity also operates in other areas of the human cerebral cortex, and if so, how it translates to regulation of behavioral performance.

In this study, we applied two different PAS protocols to induce either LTP- or LTD-like plasticity in the somatosensory cortex, followed by always the same peripheral high-frequency stimulation (pHFS) of the median nerve to induce LTP-like plasticity in the somatosensory cortex. We asked to which extent homeostatic metaplasticity governs the stimulation-induced excitability changes in the human somatosensory cortex and, in addition, investigated its behavioral correlates. We hypothesized that, according to the BCM theory, pHFS would increase excitability in the somatosensory cortex if preceded by the "PAS–LTD" protocol, but would decrease excitability if preceded by the "PAS–LTP" protocol. We hypothesized further that these changes would be accompanied by similar homeostatic regulation of tactile spatial discrimination performance.

METHODS

Subjects

We tested 19 healthy volunteers (13 women, mean age = 24.7 years, *SD* = 3.5). Subjects gave their written informed consent before participating. The study was performed in accordance with the 1964 Declaration of Helsinki and was approved by the ethics committee of the University Hospital of Frankfurt. General exclusion criteria were a history of neurological and/or psychiatric disorders, acute disease, and the intake of drugs affecting the central nervous system. All subjects were right-handed according to the Edinburgh questionnaire (Oldfield, 1971).

Experimental Design

In the main experiment, 12 subjects participated in two sessions in a pseudorandomized crossover design. The sessions were separated by at least 1 week to avoid carryover effects. We explored the effects of PAS applied to the left somatosensory cortex on changes induced by subsequent pHFS in somatosensory cortical excitability as measured by the amplitudes of median nerve somatosensory evoked cortical potentials, and in tactile spatial discrimination threshold as measured by the grating orientation task (GOT; Figure 1). In a control experiment, the effects of pHFS alone on excitability in the somatosensory cortex and tactile spatial discrimination threshold were tested in seven additional volunteers who were different from those in the main experiment (Figure 1).

Transcranial Magnetic Stimulation Procedures

Subjects were seated in a comfortable reclining chair with a mounted headrest. Focal TMS was delivered through a figure-eight coil (diameter of each wing, 70 mm) connected to a Magstim 200 magnetic stimulator (Magstim Company, Carmarthenshire, Wales, UK) with a monophasic current waveform. The coil was held tangential to the scalp with the handle directed backward and 45° away from the midline in order to induce a current flow in the brain from lateral–posterior to medial–anterior, approximately perpendicular to the central sulcus. Motor evoked potentials (MEPs) were recorded from the right abductor pollicis brevis muscle by surface electromyography (EMG), using Ag–AgCl cup electrodes in a belly–tendon montage. The EMG raw signal was amplified, band-pass filtered (20 Hz to 2 kHz; Counterpoint

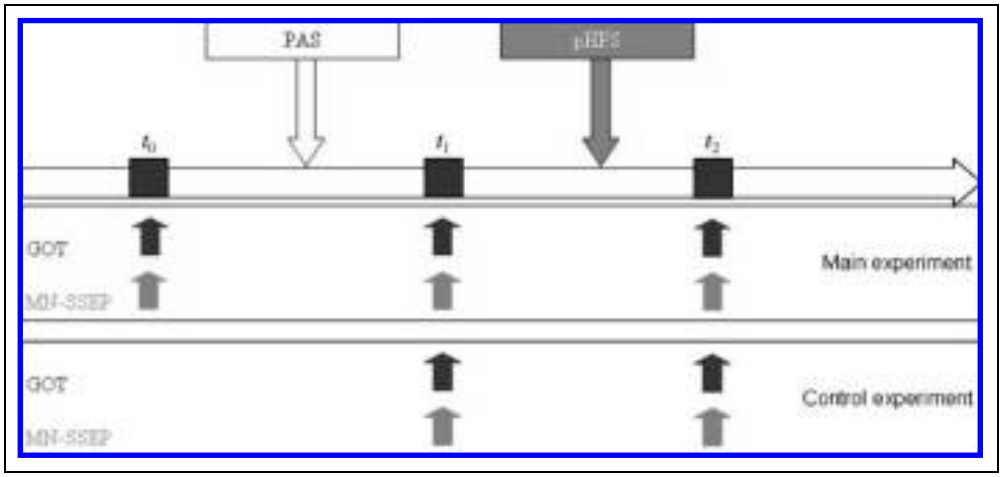

Figure 1. Experimental set-up and design. In the main experiment, PAS of the left somatosensory cortex was followed by pHFS of the right median nerve. Discrimination thresholds in the grating orientation task (GOT) and amplitudes of median nerve somatosensory evoked potentials (MN-SSEP) were assessed before (t_0) and after PAS (t_1) and after pHFS (t_2). In the control experiment, discrimination thresholds in the GOT and amplitudes of MN-SSEPs were assessed before and after pHFS without preconditioning PAS.

Mk2 electromyograph; Dantec, Skovlunde, Denmark), and digitized at an A/D rate of 5 kHz (CED Micro 1401; Cambridge Electronic Design, Cambridge, UK) using customized Spike2 software (Version 3.05, CED). The optimal coil position over the hand area of the left primary motor cortex for eliciting MEPs in the right abductor pollicis brevis muscle was determined as the site where TMS at a slightly suprathreshold stimulus intensity consistently produced the largest MEPs. This site was marked on the scalp with a soft-tip pen. At this location, resting motor threshold was determined to the nearest 1% of maximum stimulator output as the lowest stimulus intensity, which elicited MEPs ≥50 μV in at least 5 out of 10 consecutive trials.

PAS consisted of 225 pairs (rate, 0.25 Hz) of electrical stimulation of the right median nerve through a bipolar electrode (cathode proximal) using constant-current square-wave pulses (duration, 1 msec; intensity, 300% of sensory perceptual threshold) followed by TMS of the left somatosensory cortex (intensity, 150% resting motor threshold for the right abductor pollicis brevis muscle). Stimulus intensities were adopted from previous experiments (Litvak et al., 2007; Wolters et al., 2005). The target site was the primary somatosensory cortex that is located in the postcentral gyrus approximately 2 cm posterior to the precentral gyrus. Given the slightly slanting orientation of the central sulcus and the fact that the cortical motor and sensory representations of the hand are closely adjacent on both sides of the central sulcus, a position of approximately 2 cm posterior and 1 cm lateral to the motor hot spot for eliciting MEPs in the right abductor pollicis brevis muscle was chosen as stimulation site. The exact target position of TMS during PAS over the left somatosensory cortex was verified and, if necessary, adapted to individual brain anatomy using a frameless TMS navigation system (Localite TMS Navigator, Localite GmbH, Sankt Augustin, Germany) (Figure 2). Coil orientation was as described for the motor cortex above.

Two interstimulus intervals were tested, one in each session, as chosen on the basis of a previous study (Wolters et al., 2005). In that study, modeling of the experimental data suggested maximal LTP- or LTD-like changes of somatosensory cortical excitability at intervals between median nerve stimulation and the subsequent TMS pulse of the individual N20 latency minus 2.5 msec and of N20 latency minus 15 msec, respectively (cf. Figure 6 in Wolters et al., 2005). LTP- and LTD-like plasticity was demonstrated by an increase (LTP) or decrease (LTD) of the amplitude of the P25 component of the median nerve somatosensory evoked potential (Wolters et al., 2005), which most likely is generated in the superficial layers of Brodmann's area 3b of the primary somatosensory cortex (Allison, McCarthy, Wood, & Jones, 1991). Therefore, in the present study, interstimulus intervals of individual N20 latency minus 2.5 msec ($PAS_{N20-2.5}$) and individual N20 latency minus 15 msec (PAS_{N20-15}) were used to elicit LTP- and LTD-like plasticity in the somatosensory cortex, respectively.

Peripheral High-frequency Stimulation

After PAS, pHFS was applied for 20 min (Figure 1). This stimulation protocol was introduced by Ragert, Kalisch, and Dinse (2005) in the form of high-frequency peripheral tactile stimulation aiming to improve tactile acuity. In our study, pHFS consisted of trains of 20 pulses (constant-current square-wave pulse, pulse duration = 0.2 msec) of electrical median nerve stimulation at a rate of 20 Hz with an intertrain interval of 5 sec. Median nerve stimulation at the wrist was performed with a block electrode (cathode proximal). Subjects had to report a prickling phenomenon at the volar side of the thumb and index finger of the stimulated hand to verify correct positioning of the stimulating block electrode. Stimulation intensity was adjusted to 1.5 times the sensory perceptual threshold.

Median Nerve Somatosensory Evoked Potentials

Median nerve somatosensory evoked potentials were recorded and stored for off-line analysis with conventional equipment (Neuropack S1 MEB-9400, Nihon Kohden,

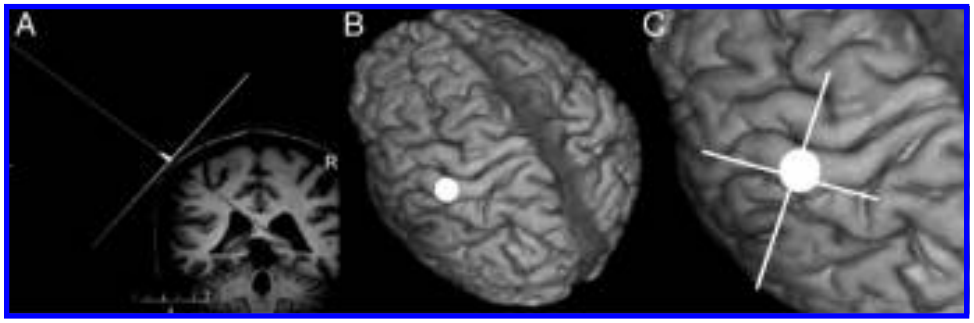

Figure 2. MRI-guided TMS. Focal TMS was applied to the somatosensory cortex (white dot in B and C on the crown of the left postcentral gyrus indicates location of the center of the figure-eight coil), approximately 2 cm posterior and 1 cm lateral to the hotspot in the primary motor cortex (not shown) for eliciting motor evoked potentials in the abductor pollicis brevis muscle of the right hand. The coil was held tangential to the scalp (cf. visualized coil axes in the coronal plane, A) with the handle directed posteriorly and 45° away from the midline (cf. visualized coil axes in axial plane, C).

band-pass filter 2 Hz–2 kHz) before PAS (time point t_0), directly after PAS (time point t_1), and directly after pHFS (time point t_2; Figure 1). One electrode (C3′) was located over the left somatosensory cortex, 2 cm posterior to C3 according to the International 10–20 system. The reference electrode was placed over the midfrontal (Fz) position. The electrodes were kept in position during PAS and pHFS. At each time point, 2 × 200 stimulus-related epochs with a sweep length of 100 msec after the stimulus were recorded. Electrical stimulation of the right median nerve was performed with a bipolar electrode at a repetition rate of 2 Hz (constant-current square-wave pulse; duration = 0.2 msec; cathode proximal). Stimulus intensity was adjusted to 2.5 times the sensory perceptual threshold and was kept constant for each subject throughout the experiment. In most subjects, the chosen stimulation intensity induced a small muscular twitch in the thenar muscles. During median nerve stimulation and somatosensory evoked potential recordings, subjects were instructed to relax but to stay awake with their eyes closed. For each block of measurements (t_0, t_1, t_2) the N20 amplitude was assessed as the difference between the baseline and the first negative peak occurring at a latency of around 17–21 msec after the time of median nerve stimulation. The amplitude of the N20–P25 complex was determined as the difference between the N20 peak and the peak of the subsequent positivity. Finally, the P25 amplitude was calculated as the difference between the amplitude of the N20–P25 complex and the N20 amplitude.

Behavioral Testing

The GOT was performed to assess behavioral consequences of the experimental manipulations. In this task, stimuli consisted of a set of seven hemispherical plastic domes with gratings cut into their surfaces, resulting in parallel bars and grooves of equal widths at each dome. As cutaneous spatial resolution is relatively insensitive to force (Johnson & Phillips, 1981) and the neural response to complex surfaces is relatively insensitive to the depth of indentation (Vega-Bermudez & Johnson, 1999), stimuli were applied at moderate force resulting in a skin indentation of approximately 2 mm. Prior to testing, the arm was immobilized and the test finger (index finger of the right hand) was fixed with adhesive tape to avoid finger movements during the test. Each subject was taught the task by visual demonstration of the stimuli. On a given trial, the gratings were applied to the distal pad of the test finger for approximately 1 sec with the ridges and grooves randomly oriented in one of two orthogonal directions, either perpendicular or parallel to the axis of the finger. Starting with the grating with the broadest spatial period and thereafter continuing in a descending groove width order, subjects had to identify and verbally report the alignment in blocks of 20 trials until performance dropped below 75% correct responses. Performance at this level lies midway between chance and perfect performance and is a standard psychophysical criterion for tactile acuity threshold determination (Van Boven & Johnson, 1994). Absolute discrimination thresholds were calculated as follows:

$$\text{Threshold}_{G75} = G_{\text{below}} + ((0.75 - P_{\text{below}})/(P_{\text{above}} - P_{\text{below}}))(G_{\text{above}} - G_{\text{below}})$$

where Threshold_{G75} depicts the estimated threshold for the grating spacing on which the subject scored 75% correct responses; G represents the grating spacing; P equals the probability of correct answer, "below" describes the grating spacing or probability of correct response on the highest grating spacing on which the subject responded correctly less than 75% of the time; "above" describes the grating spacing or probability of a correct response on the lowest grating spacing on which the subject responded correctly more than 75% of the time.

To familiarize subjects with the GOT, they performed a practice session (in blocks of 20 trials until discrimination threshold was reached) prior to each experimental session. During the main experiment, two sessions were run before PAS (t_0), one session after PAS (t_1), and one session after pHFS (t_2), respectively. The mean GOT threshold from the two sessions before PAS served as baseline. In the control experiment, the effect of pHFS alone on the threshold in the GOT was tested. Here, two sessions of GOT were done prior to and one session after pHFS (Figure 1).

Data Analysis

In the main experiment, median nerve somatosensory evoked cortical potential and GOT data were normalized to baseline values (before experimental manipulation, time point t_0) and entered in a two-way repeated measures analysis of variance (rmANOVA) with the within-subjects factors time (t_1, t_2) and type of preconditioning (condition: $\text{PAS}_{\text{N20}-15}$, $\text{PAS}_{\text{N20}-2.5}$). In case of significant main effects, post hoc two-tailed paired-samples or one-sample t tests were performed.

In order to evaluate homeostatic metaplasticity, the correlation between changes in individual median nerve somatosensory evoked cortical potential amplitude induced by pHFS and by the conditioning PAS was assessed by linear regression analysis. Homeostatic metaplasticity would be indicated by a negative correlation (Müller et al., 2007). The same analysis was also performed for GOT thresholds.

Effects of pHFS alone on median nerve somatosensory evoked cortical potentials and tactile spatial discrimination threshold were explored in the control experiment. These data were compared with those in the main experiment by a one-way ANOVA with the between-subjects factor condition (pHFS alone, pHFS preconditioned by

PAS_{N20-15}, pHFS preconditioned by $PAS_{N20-2.5}$). Data from the main experiment were normalized to the time point t_1 prior to pHFS. In case of significant main effects, post hoc two-tailed unpaired-samples t test was applied. For all tests, significance was assumed if $p < .05$. Data are reported as means ± *SEM*.

RESULTS

Main Experiment

Excitability in the Somatosensory System

We found that changes in excitability of the somatosensory cortex after high-frequency median nerve stimulation were dependent on the type of PAS used as preconditioning stimulation. This was indicated by a significant Condition × Time interaction for P25 [$F(1, 11) = 8.48, p = .01$] and N20–P25 amplitudes [$F(1, 11) = 7.03, p = .02$] (Figure 3A, B), but not for N20 amplitudes [Condition × Time: $F(1, 11) = 0.43, p = .53$]. *Post hoc* testing revealed that $PAS_{N20-2.5}$ and PAS_{N20-15} had no significant effect on the P25 ($PAS_{N20-2.5}$, $p = .80$; PAS_{N20-15}, $p = .064$) or N20–P25 amplitude ($PAS_{N20-2.5}$, $p = .72$; PAS_{N20-15}, $p = .053$). Despite this lack of effects on somatosensory cortical excitability, PAS preconditioning had a differential impact on the effects induced by subsequent high-frequency median nerve stimulation (pHFS). If preconditioned by $PAS_{N20-2.5}$, pHFS induced a significant decrease in the P25 ($p = .01$) and N20–P25 amplitudes ($p = .01$), whereas pHFS preconditioned by PAS_{N20-15} produced nonsignificant trends toward increases in P25 ($p = .11$) and N20–P25 amplitudes ($p = .19$) (Figure 3A, B). P25 and N20–P25 amplitudes at baseline were not different between PAS conditions (P25 before $PAS_{N20-2.5} = 2.10 \pm 0.30$ μV vs. P25 before $PAS_{N20-15} = 2.08 \pm 0.29$ μV; N20–P25 before $PAS_{N20-2.5} = 3.29 \pm 0.30$ μV vs. N20–P25 before $PAS_{N20-15} = 3.30 \pm 0.35$ μV; all $p > .9$), and therefore, cannot account for the observed Condition × Time interactions.

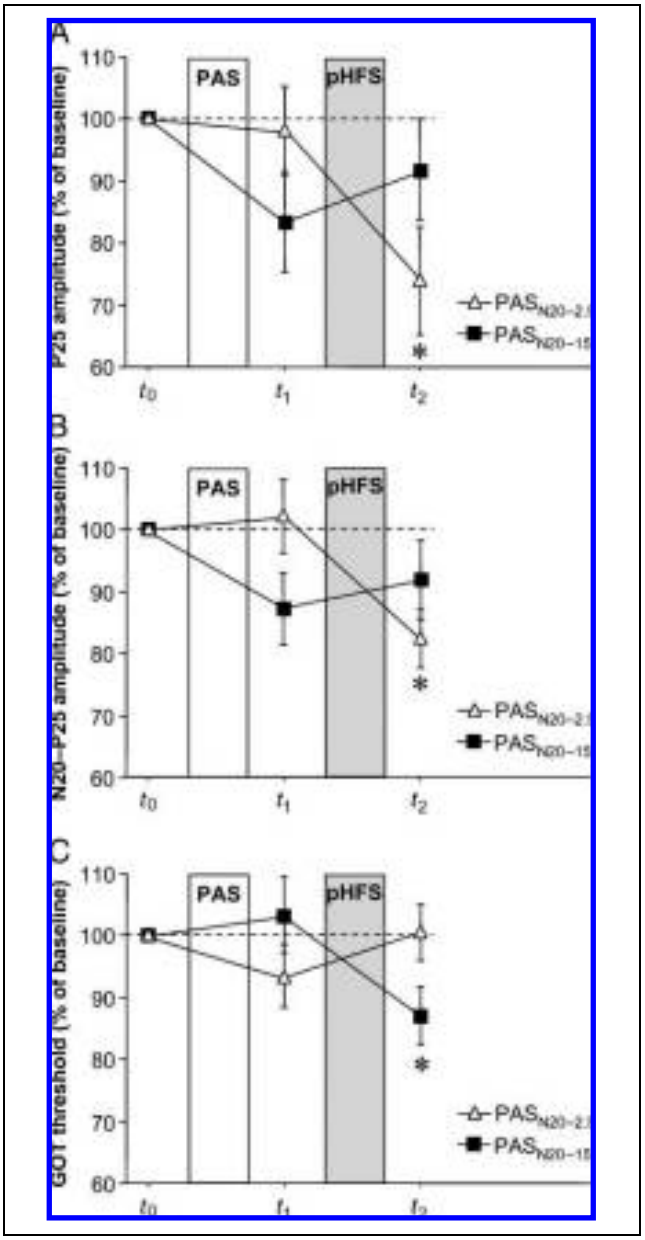

Figure 3. Changes in somatosensory cortical excitability (N20–P25 and P25 amplitudes) and tactile spatial discrimination, assessed by the GOT threshold. PAS had no significant effect on amplitudes of (A) the P25 and (B) the N20–P25 component of the median nerve somatosensory evoked potential, or (C) on the GOT threshold. After preconditioning with $PAS_{N20-2.5}$ (open triangles), pHFS significantly decreased P25 and N20–P25 amplitudes (A, B). After preconditioning with PAS_{N20-15}, pHFS decreased GOT threshold, whereas after $PAS_{N20-2.5}$, pHFS resulted in a trend toward an increase in GOT threshold. Asterisks indicate significant pHFS effects (paired-sample t tests, $p \leq .01$). All data are normalized to time point t_0 (baseline prior to PAS) and are means ± 1 *SEM*.

Tactile Spatial Discrimination Thresholds

The main experiment further showed that tactile spatial discrimination thresholds were differentially modified by high-frequency median nerve stimulation (pHFS), that is, the direction of changes in tactile spatial discrimination depended on the type of PAS preconditioning as indicated by a significant Condition × Time interaction for tactile discrimination threshold [$F(1, 11) = 10.59$, $p = .008$] (Figure 3C). Post hoc testing revealed that tactile spatial discrimination thresholds remained unchanged by PAS (PAS_{N20-15}, $p = .60$; $PAS_{N20-2.5}$, $p = .22$). pHFS significantly decreased tactile spatial discrimination threshold if preconditioned by PAS_{N20-15} ($p = .008$), whereas pHFS resulted in a nonsignificant trend toward an increase in tactile spatial discrimination threshold if preconditioned by $PAS_{N20-2.5}$ ($p = .14$) (Figure 3C). There was no difference in the tactile spatial discrimination threshold at baseline between the two PAS conditions (before $PAS_{N20-2.5} = 1.24 \pm 0.09$ mm vs. before $PAS_{N20-15} = 1.34 \pm 0.15$ mm, $p = .40$) that could have accounted for the differential effects of pHFS on tactile spatial discrimination threshold.

Correlation Analyses

The change in N20–P25 amplitude induced by pHFS was significantly negatively correlated with the change in N20–P25 amplitude induced by the preconditioning PAS (Pearson's correlation, $r = -.53$, $p = .008$) (Figure 4A). A similar negative linear correlation was found for changes in tactile spatial discrimination threshold ($r = -.57$, $p = .004$) (Figure 4B).

The changes in N20–P25 amplitude induced by pHFS were not significantly correlated with changes in tactile spatial discrimination threshold ($r = -.37$, $p = .08$).

Control Experiment

In the control experiment, the effects of pHFS alone on excitability of the somatosensory cortex and tactile spatial discrimination threshold were investigated in an additional group of seven healthy subjects. These were compared with the effects of pHFS conditioned by PAS_{N20-15} or $PAS_{N20-2.5}$ in the main experiment.

With respect to the P25 amplitude, the one-way ANOVA revealed a significant effect of condition [$F(2) = 5.91$, $p = .0072$], which was explained by significant differences between pHFS alone versus pHFS preconditioned by $PAS_{N20-2.5}$ ($p = .009$), and pHFS preconditioned by PAS_{N20-15} versus pHFS preconditioned by $PAS_{N20-2.5}$ ($p = .006$), whereas effects by pHFS alone versus pHFS preconditioned by PAS_{N20-15} were not different ($p = .83$) (Figure 5A). Only pHFS preconditioned by $PAS_{N20-2.5}$ resulted in a significant change (decrease) of the P25 amplitude ($p = .009$) whereas changes produced by pHFS alone and pHFS preconditioned by PAS_{N20-15} were not significant ($p > .1$) (Figure 5A).

Similar observations were made for the N20–P25 amplitude. The ANOVA revealed a significant effect of condition [$F(2) = 6.13$, $p = .0062$], which was explained by significant differences between pHFS alone versus pHFS preconditioned by $PAS_{N20-2.5}$ ($p = .010$) and pHFS preconditioned by PAS_{N20-15} versus pHFS preconditioned by $PAS_{N20-2.5}$ ($p = .004$), whereas effects by pHFS alone versus pHFS preconditioned by PAS_{N20-15} were not different ($p = .93$) (Figure 5B). Only pHFS preconditioned by $PAS_{N20-2.5}$ resulted in a significant change (decrease) of the N20–P25 amplitude ($p = .007$), whereas changes produced by pHFS alone and pHFS preconditioned by PAS_{N20-15} were not significant ($p > .15$) (Figure 5B). The absolute P25 and N20–P25 amplitudes prior to pHFS were not different across conditions (P25: pHFS alone = 1.53 ± 0.34 μV, pHFS preconditioned by PAS_{N20-15} = 1.72 ± 0.30 μV, pHFS preconditioned by $PAS_{N20-2.5}$ = 2.03 ± 0.27 μV; N20–P25: pHFS alone = 2.76 ± 0.40 μV, pHFS preconditioned by PAS_{N20-15} = 2.84 ± 0.36 μV, pHFS preconditioned by $PAS_{N20-2.5}$ = 3.33 ± 0.31 μV; all $p > .25$) and therefore cannot account for these differential effects of pHFS on the P25 and N20–P25 amplitudes.

For tactile spatial discrimination threshold, the one-way ANOVA also revealed a significant effect of condition [$F(2) = 8.33$, $p = .0015$], which was explained by significant differences between pHFS alone versus pHFS preconditioned by $PAS_{N20-2.5}$ ($p = .006$) and pHFS preconditioned by PAS_{N20-15} versus pHFS preconditioned by $PAS_{N20-2.5}$ ($p = .0007$), whereas effects by pHFS alone versus pHFS preconditioned by PAS_{N20-15} were not different ($p = .77$) (Figure 5C). pHFS alone and pHFS preconditioned by PAS_{N20-15} resulted in a significant decrease of the tactile spatial discrimination threshold ($p = .017$ and $p = .0044$, respectively), whereas pHFS preconditioned by $PAS_{N20-2.5}$ did not significantly change threshold ($p = .11$) (Figure 5C). The absolute tactile spatial discrimination thresholds prior to pHFS were not different across conditions (pHFS alone = 1.31 ± 0.08 mm, pHFS preconditioned by PAS_{N20-15} = 1.38 ± 0.16 mm, pHFS preconditioned by $PAS_{N20-2.5}$ = 1.13 ± 0.07 mm, all $p > .1$), and therefore, do not explain the observed differential effects of pHFS.

DISCUSSION

The principal novel finding of this study is that consecutive application of PAS targeting the somatosensory

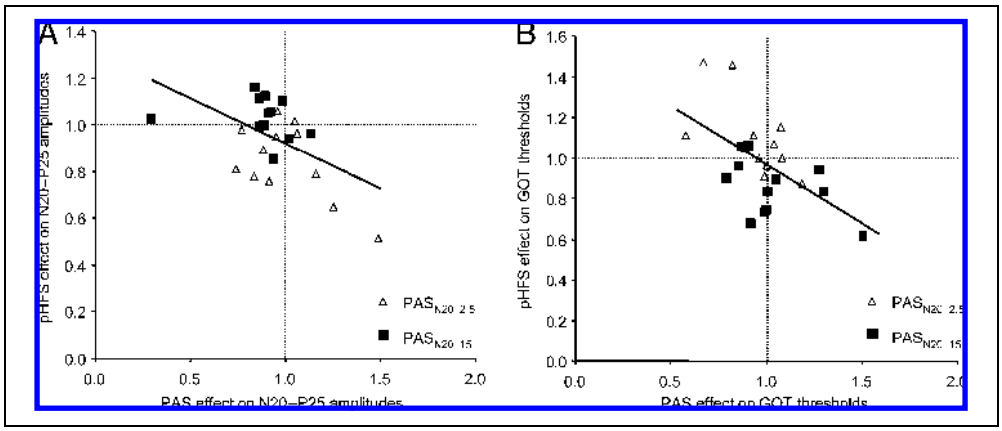

Figure 4. Correlation between effects induced by PAS and subsequent pHFS on N20–P25 amplitudes (A) and threshold in the GOT (B). An increase in N20–P25 amplitudes after PAS (values >1.0) was associated with a decrease in N20–P25 amplitude after pHFS (values < 1.0; Pearson's correlation $r = -.53$, $p = .008$). A similar negative linear correlation was found for changes in GOT threshold ($r = -.57$, $p = .004$). All data are normalized to values prior to PAS (*x*-axis) or prior to pHFS (*y*-axis).

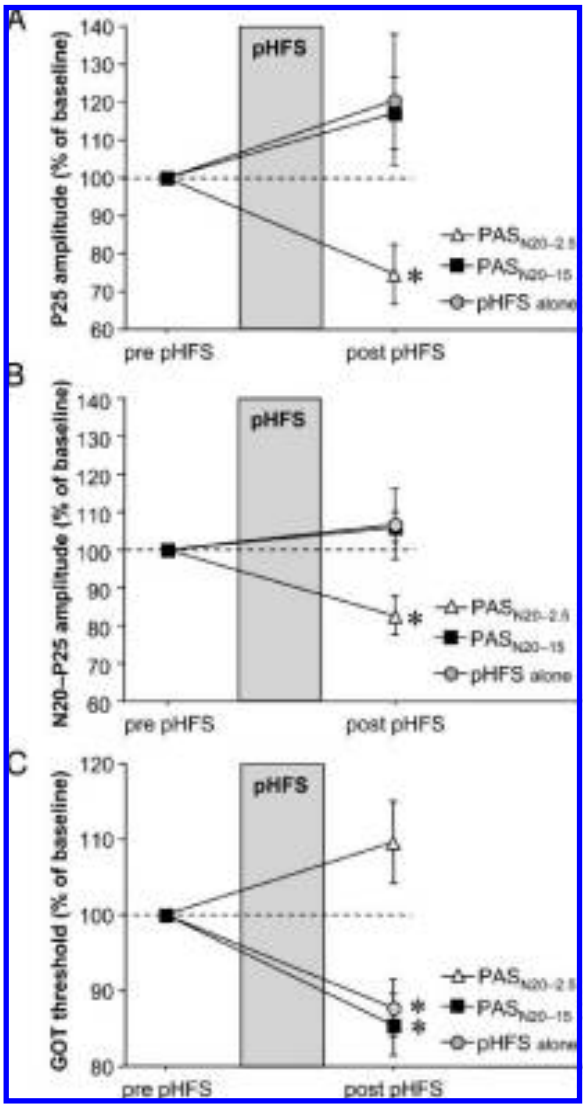

Figure 5. Changes in somatosensory cortical excitability (P25 and N20–P25 amplitudes, A–B) and in tactile spatial discrimination (GOT threshold, C) induced by pHFS alone (control experiment, gray circles), or by pHFS preconditioned by paired associative stimulation (data from the main experiment PAS_{N20-15}, black squares; $PAS_{N20-2.5}$, open triangles). Note that all effects of pHFS alone and pHFS preconditioned by PAS_{N20-15} were very similar but significantly different from those of pHFS preconditioned by $PAS_{N20-2.5}$ (unpaired t tests, all $p \leq .01$). Asterisks indicate significant pHFS effects (one-sample t tests, $p < .02$). All data are normalized to measurements prior to pHFS and are means ± 1 *SEM*.

cortex followed by high-frequency stimulation of median nerve (pHFS) revealed changes in excitability of the somatosensory cortex (measured by the N20–P25 and P25 components of the median nerve somatosensory evoked cortical potential) and tactile spatial discrimination (measured by the GOT threshold) that closely follow the rules of homeostatic metaplasticity. PAS per se had no significant overt impact on somatosensory cortical excitability or tactile spatial discrimination threshold. However, the direction of effects induced by subsequent pHFS varied with the preconditioning PAS protocol: after PAS_{N20-15}, excitability tended to increase and tactile spatial discrimination threshold decreased. After $PAS_{N20-2.5}$, excitability decreased and discrimination threshold tended to increase.

PAS in the Human Somatosensory Cortex

PAS can induce bidirectional changes in somatosensory cortical excitability (Wolters et al., 2005). These are contingent upon near-synchronicity of the events in the somatosensory cortex caused by median nerve stimulation and TMS, and the direction of change is critically dependent on the exact interval between the two stimuli. TMS applied at −5 msec, −2.5 msec, and 0 msec relative to the individual N20 latency induced a long-lasting LTP-like increase in the amplitude of the P25 component of the median nerve somatosensory evoked potential, whereas TMS applied 20 msec before the individual N20 latency significantly decreased the P25 amplitude (Wolters et al., 2005). The LTP-like changes after $PAS_{N20-2.5}$, but not the LTD-like changes after PAS_{N20-20}, were recently reproduced by the same group (Litvak et al., 2007). These findings could not be replicated in the present study, although two interstimulus intervals between median nerve stimulation and TMS were used, which according to the previous experimental data and modeling (cf. Figure 6 in Wolters et al., 2005) were expected to induce maximal LTP- ($PAS_{N20-2.5}$) or LTD-like (PAS_{N20-15}) plasticity. The experimental protocol differed slightly from the ones previously used (Litvak et al., 2007; Wolters et al., 2005). We applied 225 pairs of stimuli at a rate of 0.25 Hz for a period of 15 min, whereas previously fewer stimuli (180 pairs) were given at a lower rate (0.1 Hz). As changes in median nerve somatosensory evoked potential amplitudes in general were subtle, and the effect size in the previous studies was rather small (in the order of 10% or less) and, in part, not reproducible, it is well possible that the small differences between the experimental protocols accounted for the lack of overt change in somatosensory cortical excitability after PAS in the present study.

In addition, we were unable to confirm the recent findings by Litvak et al. (2007), who found a significant improvement of two-point discrimination after the PAS_{N20-20} protocol in the absence of significant change in somatosensory cortical excitability. Further, they observed a nonsignificant trend toward impairment in tactile two-point discrimination after the $PAS_{N20-2.5}$ protocol, which induced an LTP-like increase in somatosensory cortical excitability. This disparity of results presented by Litvak et al. and of those in the current study may again be explained by the slight differences in the PAS protocols, but certainly also by the fact that different tests were applied to assess tactile discrimination performance.

Others have shown consistently that tactile discrimination performance deteriorates after low-frequency (1 Hz) rTMS (Tegenthoff et al., 2006; Knecht et al., 2003) and improves after high-frequency (5 Hz) rTMS (Pleger et al., 2006; Tegenthoff et al., 2005) or high-frequency rTMS paired with peripheral tactile stimulation (Ragert et al., 2003). Similarly, operant learning of tactile spatial discrimination can be enhanced by concurrent high-frequency rTMS of the somatosensory cortex (Karim, Schuler, Hegner, Friedel, & Godde, 2006). However, changes in the excitability of the somatosensory cortex were not assessed in these studies by means of median nerve somatosensory evoked potential amplitudes. Low-frequency rTMS applied to the hand area of the primary motor cortex decreases consistently motor cortical excitability as expressed by MEP amplitude and high-frequency rTMS increases it (for review, Ziemann, 2004; Classen & Ziemann, 2003). It is not clear though whether this dichotomy of effects also applies when rTMS is directed to other cortical areas. At least, low-frequency (1 Hz) rTMS (Enomoto et al., 2001) and intermittent theta-burst stimulation of the somatosensory cortex with the initial phase of current in the brain directed latero-posteriorly (Katayama & Rothwell, 2007) failed to alter median nerve somatosensory evoked potential amplitudes.

Homeostatic Interactions between PAS and pHFS on Somatosensory Cortical Excitability

Homeostatic metaplasticity is currently thought to constitute a fundamental principle in order to enable both selective modification and maintenance of synaptic strength in a physiological range (Abbott & Nelson, 2000; Abraham & Tate, 1997). A theoretical account for homeostatic metaplasticity has been given by the BCM rule, which proposes that synaptic plasticity is bidirectional (LTP vs. LTD) and depends on a combined function of pre- and postsynaptic activity (Bienenstock et al., 1982). Importantly, the LTP/LTD induction threshold is sliding as a function of the time-averaged postsynaptic activity. Thus, a previously high level of postsynaptic activity facilitates LTD induction, whereas a previously low level of postsynaptic activity facilitates LTP induction (Bear, 1995; Bienenstock et al., 1982).

Given the significant impact of PAS on the subsequent pHFS effects in the present study (Figures 3 and 4), it has to be assumed that PAS induced a relevant priming effect in the somatosensory cortex, the direction of which was critically dependent on the interval between the median nerve stimulus and TMS of the contralateral somatosensory cortex: pHFS tended to increase somatosensory cortical excitability if preconditioned by PAS_{N20-15}, but decreased excitability if preconditioned by $PAS_{N20-2.5}$. The lack of overt effects of PAS on somatosensory cortical excitability per se but its significant modulating effect on the subsequent pHFS effects is reminiscent of similar observations in slices of hippocampus where a priming stimulation that precedes high-frequency stimulation can inhibit the subsequent induction of LTP for several minutes (Gisabella et al., 2003; Huang et al., 1992) without persistent changes in the synaptic response by the priming stimulation itself (Huang et al., 1992).

The present effects are consistent with spike-timing dependent plasticity in the primary somatosensory cortex (Feldman, 2000), where associative LTP at synapses from cortical layer 4 to layers 2/3 occurs if excitatory postsynaptic potentials systematically lead action potentials in the postsynaptic cell, whereas LTD occurs if this order of events is reversed (Feldman, 2000). In the present PAS experiments, excitatory postsynaptic potentials are thought to be generated by the afferent signal from median nerve stimulation and action potentials in neurons of the somatosensory cortex by suprathreshold TMS. Accordingly, with the interval N20 − 15 msec, action potentials lead excitatory postsynaptic potentials and this results in depression (even if not directly measurable here), whereas with the interval N20 − 2.5 msec, near coincidence of the events caused by median nerve stimulation and TMS in the somatosensory cortex can be assumed (Wolters et al., 2005), resulting in potentiation. Similar PAS effects that adhere to the rules of spike-timing dependent plasticity have been described in the human primary motor cortex (Müller et al., 2007; Weise et al., 2006; Ziemann et al., 2004; Wolters et al., 2003).

Peripheral tactile stimulation can change tactile discrimination performance in a frequency specific manner. High-frequency tactile stimulation improved tactile spatial discrimination, whereas low-frequency stimulation at a rate of 1 Hz impaired it (Ragert et al., 2005). In the present protocol, pHFS in the form of electrical stimulation of the median nerve rather than tactile stimulation of the index finger was chosen in order to activate exactly the same afferent pathway as in PAS. Therefore, it can be assumed that any interactions between the effects induced by the two stimulation protocols occurred within the same neuronal circuit, most likely even at the same synapses, in cortical layers 2/3 of the somatosensory cortex (see below). The amount of improvement in tactile spatial discrimination threshold (13.2 ± 3.8%) by high-frequency electrical stimulation of median nerve was very similar to the one described previously by Ragert and colleagues when high-frequency tactile stimulation was used (14.0 ± 3.3%). Homeostatic metaplasticity at single synapses has been described in hippocampal (Huang et al., 1992) and cortical slices (Volgushev, Mittmann, Chistiakova, Balaban, & Eysel, 1999) and is being referred to as homosynaptic homeostatic metaplasticity. Homosynaptic-like homeostatic metaplasticity has been demonstrated recently in the human motor cortex by showing that two identical subsequent PAS protocols that can be assumed to activate the same neuronal cortical circuits and synapses interact in a homeostatic manner (Müller et al., 2007).

The present study provides evidence for the first time that homeostatic mechanisms also operate in the human somatosensory cortex. This suggests that homeostatic metaplasticity constitutes a general principle in the human cerebral cortex to maintain synaptic strength in a physiological range. It is commonly accepted that both the N20 and the P25 components of the median nerve somatosensory evoked potential are generated in the posterior bank of the central sulcus, corresponding to Brodmann's area 3b (Huang et al., 2000; Mauguiere et al., 1999; Lee & Seyal, 1998; Urbano et al., 1997; McLaughlin & Kelly, 1993; Allison et al., 1989). Therefore, it can be assumed that changes in the P25 component indicate excitability changes in the primary somatosensory cortex. The N20 component most probably reflects the passive source current for active depolarizing sinks on the cell bodies and proximal apical dendrites of pyramidal cells in layer 4, whereas the P25 is thought to be generated by depolarization of the superficial portion of apical dendrites located in cortical layers 2/3 (Allison et al., 1991). As changes were observed only for the P25 component but not the N20 component in this study, it follows that the synaptic plasticity induced by pHFS and its homeostatic interactions with the preceding PAS most likely took place in cortical layers 2/3. A subcortical contribution to the observed effects is rather unlikely, as it would have equally affected N20 and P25 amplitudes. These results are in line with animal experiments showing homeostatic mechanisms of cortical map plasticity in the primary somatosensory cortex after sensory deprivation. There is evidence that LTD drives the rapid, activity-dependent reduction of responses to deprived or behaviorally irrelevant sensory stimuli within the somatosensory cortex (Allen, Celikel, & Feldman, 2003; Glazewski & Fox, 1996). After sensory deprivation, further LTD was shown to be occluded, whereas LTP was enhanced in feed-forward projections from layer 4 to layers 2/3 (Allen et al., 2003).

As stimulation intensity in the present study was relatively high (150% of resting motor threshold), it cannot be entirely ruled out that PAS induced excitability changes in adjacent areas such as the primary motor cortex. In a control experiment, Wolters et al. (2005) found that P25 amplitudes were only increased when PAS_{N20} targeted the somatosensory cortex but not when PAS_{N20} targeted the primary motor cortex. This renders it rather unlikely that the PAS effects observed in the present study were a result of an activation of neuronal elements in the primary motor cortex. In addition, the specific timing of median nerve and TMS in the current PAS protocol was chosen to reflect spike-timing dependent plasticity in the somatosensory cortex and not in the motor cortex. As previously described, the time point of equilibrium with respect to interstimulus interval between enhancing and depressing effects on excitability in the somatosensory cortex is 6.8 msec earlier than in the motor cortex, and $PAS_{N20-2.5}$ would not be expected to result in significant plasticity in the motor cortex (cf. Figure 6 in Wolters et al., 2005). In summary, given the specific action on the P25 component of the median nerve somatosensory evoked potential which is generated in cortical layers 2/3 of area 3b of the primary somatosensory cortex, the lack of effects on somatosensory evoked cortical potential components when PAS was applied to the primary motor cortex (Wolters et al., 2005), and the timing of stimuli which was specifically adopted to serve spike-timing plasticity in the somatosensory cortex, we are confident that the observed plastic changes and their interactions took place in the stimulated somatosensory cortex rather than in other brain areas.

Homeostatic Interactions between PAS and pHFS on Tactile Spatial Discrimination Performance

The present study shows that homeostatic mechanisms govern not only changes in somatosensory cortical excitability but also, in a parallel manner, changes in somatosensory behavioral performance. So far, little is known about how homeostatic metaplasticity influences behavior. Ziemann et al. (2004) were the first to address this issue in the motor domain by demonstrating a homeostatic interaction between motor learning and the subsequent induction of LTP- and LTD-like plasticity in human M1. Intense practice of fastest possible thumb abduction movements prevented a subsequent PAS protocol from inducing an LTP-like increase in motor cortical excitability, whereas it enhanced PAS-induced LTD-like plasticity. This served as a strong argument that motor learning in humans is an LTP-dependent process. According to the characteristics of homeostatic metaplasticity, it can be predicted from these findings that LTP-dependent behavioral processes will be enhanced when preconditioned by a stimulation protocol that induces LTD-like plasticity, and this is, indeed, supported by recent preliminary data on motor learning preconditioned by PAS (Ziemann, Ilic, & Jung, 2006). In line with these findings in the motor cortex, the current data provide evidence that the pHFS-induced changes in tactile spatial discrimination threshold were similarly modulated in a homeostatic fashion by preconditioning PAS. Several lines of evidence strongly suggest that improvement in tactile spatial discrimination performance driven by peripheral stimulation reflects LTP-like representational plasticity in the somatosensory cortex: (1) the magnitude of improvement in tactile spatial discrimination correlated directly with the magnitude of quantitative measures of map reorganization in the somatosensory cortex (Dinse, Ragert, Pleger, Schwenkreis, & Tegenthoff, 2003; Pleger et al., 2001, 2003); (2) its duration is in the order of 2–4 hr (Godde, Stauffenberg, Spengler, & Dinse, 2000); and (3) the improvement of tactile spatial discrimination can be blocked by antagonists at the *N*-methyl-D-aspartate receptor (Dinse et al., 2003). Therefore, the failure of

pHFS to induce improvement in tactile spatial discrimination if preconditioned by $PAS_{N20-2.5}$ can be interpreted as a homeostatic interaction of two subsequent LTP-dependent processes.

Importantly, in this study, we did not observe a direct relationship between changes in somatosensory cortical excitability and improvement in tactile spatial discrimination. Changes in cortical excitability did not significantly correlate with changes in spatial discrimination performance. In addition, the P25 amplitude did not change after pHFS alone or pHFS preconditioned by PAS_{N20-15}, whereas tactile spatial discrimination improved. Although several authors suggested a close link between excitability changes and behavior (Höffken et al., 2007; Dinse et al., 2003), this view might be overly simplistic. There is no a priori reason for performance improvement to be more closely linked to LTP than to LTD as both mechanisms contribute to the coding of information in the brain (Martin, Grimwood, & Morris, 2000). In addition, improvement in one behavioral task does not exclude that others at the same time are even impaired. For instance, Hodzic, Veit, Karim, Erb, and Godde (2004) demonstrated that tactile spatial discrimination improved after tactile coactivation—a protocol that has recently been shown to increase excitability in the somatosensory system (Höffken et al., 2007), whereas tactile temporal discrimination at the same time declined (Hodzic et al., 2004). This suggests that the relation between excitability in the somatosensory system and behavioral measures of somatosensory performance is not necessarily simple and will require further investigation.

Control Experiment

The magnitude of improvement in tactile spatial discrimination induced by pHFS preconditioned by PAS_{N20-15} did not differ from the one induced by pHFS alone (Figure 5C). There are three possible explanations for this lack of difference: (1) PAS_{N20-15} simply had no conditioning effect; (2) the improvement in tactile spatial discrimination was saturated by pHFS alone and could not be enhanced further; (3) the trend toward decreased somatosensory cortical excitability after PAS_{N20-15} (cf. Figure 3A, B) may have exerted a negative gating effect that interfered with the expected homeostatic interaction, with the net result of no difference to the pHFS alone condition. Similar observations were made previously in the motor cortex where a preconditioning PAS–LTD protocol failed to enhance subsequent PAS-induced LTP-like plasticity when compared to LTP-like plasticity induced by PAS–LTP alone (Müller et al., 2007). Although we cannot further distinguish between these possibilities, it is important to note that the lack of difference between the pHFS alone and pHFS preconditioned by PAS_{N20-15} protocols on improvement of tactile spatial discrimination does, by no means, take anything away from the main finding of this work, that is, a homeostatic regulation of somatosensory cortical excitability and tactile spatial discrimination threshold, because it remains true that the effects of pHFS preconditioned by $PAS_{N20-2.5}$ on excitability and threshold differed significantly from those of pHFS alone and pHFS preconditioned by PAS_{N20-15} in accord with the theory of homeostatic metaplasticity.

Behavioral Relevance

The spatial structure of objects contacting the skin is essential for the extraction of form and texture (Johnson, Yoshioka, & Vega-Bermudez, 2000). Impaired spatial acuity at the fingertips may translate into great difficulties in tasks requiring fine manipulations (Tremblay, Wong, Sanderson, & Cote, 2003). Manual dexterity strongly depends on tactile perceptual capacities. Hence, experimental interventions capable of modulating tactile spatial discrimination may be utilized for therapeutic use after sensory loss to improve hand function. The present results suggest that it may be particularly possible to scale down exaggerated representational plasticity in the somatosensory cortex that is unwanted or even maladaptive, such as in chronic deafferentation pain (Flor et al., 1995).

To conclude, the current work supports the view that homeostatic mechanisms play an important role in regulating plasticity in the intact human somatosensory cortex. Further, this study shows, for the first time, that homeostatic metaplasticity of cortical excitability is paralleled by homeostatic metaplasticity of a behavioral measure.

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