A Temporally Asymmetric Hebbian Rule Governing Plasticity in the Human Motor Cortex

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Submitted 8 October 2002; accepted in final form 18 January 2003

Wolters, Alexander, Friedhelm Sandbrink, Antje Schlottmann, Erwin Kunesch, Katja Stefan, Leonardo G. Cohen, Reiner Benecke, and Joseph Classen. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. J Neurophysiol 89: 2339–2345, 2003. First published January 22, 2003; 10.1152/jn.00900.2002. Synaptic plasticity is conspicuously dependent on the temporal order of the pre- and postsynaptic activity. Human motor cortical excitability can be increased by a paired associative stimulation (PAS) protocol. Here we show that it can also be decreased by minimally changing the interval between the two associative stimuli. Corticocortical excitability of the abductor pollicis brevis (APB) representation was tested before and after repetitively pairing of single right median nerve stimulation with single pulse transcranial magnetic stimulation (TMS) delivered over the optimal site for activation of the contralateral APB. Following PAS, depression of TMS-evoked motor-evoked potentials (MEPs) was induced only when the median nerve stimulation preceded the TMS pulse by 10 ms, while enhancement of cortical excitability was induced using an interstimulus interval of 25 ms, suggesting an important role of the sequence of cortical events triggered by the two stimulation modalities. Experiments using F-wave studies and electrical brain stem stimulation indicated that the site of the plastic changes underlying the decrease of MEP amplitudes following PAS (10 ms) was within the motor cortex. MEP amplitudes remained depressed for approximately 90 min. The decrease of MEP amplitudes was blocked when PAS(10 ms) was performed under the influence of dextromethorphan, an N-methyl-D-aspartate-receptor antagonist, or nimodipine, an L-type voltage-gated calcium-channel antagonist. The physiological profile of the depression of human motor cortical excitability following PAS(10 ms) suggests long-term depression of synaptic efficacy to be involved. Together with earlier findings, this study suggests that strict temporal Hebbian rules govern the induction of long-term potentiation/long-term depression-like phenomena in vivo in the human primary motor cortex.

INTRODUCTION

Activity-dependent long-term modification of synaptic efficacy has been proposed to underlie information storage in neuronal populations. Hebb (1949) postulated that the strength of a synapse may be modulated by correlated activity of a (weak) input to a postsynaptic cell with activation of that cell, as a consequence of activity of another (strong) input to it. This principle, termed associativity, has been confirmed experimentally in numerous studies. Additionally, a stringent and surprisingly simple asymmetric temporal rule governing the direction of synaptic change has been revealed in many brain regions. With few notable exceptions (e.g., Bell et al. 1997; Egger et al. 1999; Holmgren and Zilberter 2001), it was found that associative long-term potentiation (LTP) was induced when an action potential of the postsynaptic neuron (induced by a strong input to the cell) followed the postsynaptic potential induced by a weak input. If the order of stimulation was reversed (i.e., postsynaptic neuron firing an action potential before the weak input), long-term depression (LTD) of the weak input was induced (Bi and Poo 1998; Debanne et al. 1998; Feldman 2000; Gustafsson et al. 1987; Levy and Steward 1983; Magee and Johnston 1997; Markram et al. 1997; Zhang et al. 1998). This spike-timing-dependent plasticity rule fulfills the theoretical requirement of Hebbian learning for competition among synapses (Miller 1996) and represents an attractive principle which could explain important features of plasticity in developing as well as in mature cortex (Song and Abbott 2001).

While most induction studies investigating the temporal rules of bidirectional modulation of synaptic efficacy [LTP/LTD] have been performed on cultured neurons or in vitro brain slice preparations, few studies have been done in vivo (Zhang et al. 1998), and in the intact adult cortex (Fu et al. 2002; Yao and Dan 2001). In particular, physiological evidence of whether a temporally asymmetric Hebbian (TAH) rule (Paulsen and Sejnowski 2000) is operative in changing synaptic efficacy in executive brain regions is lacking in humans.

Plasticity in the human motor cortex can be elicited using an intervention shaped after models of associative LTP in experimental animals (Stefan et al. 2000). Low-frequency median nerve stimulation was paired with transcranial magnetic stimulation (TMS) over the contralateral motor cortex representing the abductor pollicis brevis muscle (APB). TMS leads to transynaptic excitation of cortical output neurons (Rothwell 1997) and some of the somatosensory afferent information

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evoked by median nerve stimulation reaches the primary motor cortex in a highly somatotopically organized fashion (Classen et al. 2000; Rosén and Asanuma 1972). This protocol, termed paired associative stimulation (PAS), rapidly induced a long-lasting, reversible, and topographically specific increase in the amplitudes of motor-evoked potentials (MEPs) evoked by TMS in the resting APB that was dependent on NMDA-receptor activation (Stefan et al. 2000, 2002). Considering these properties, we have proposed that the PAS-induced plasticity may be related to associative LTP of cortical synapses in the human cortex (Stefan et al. 2000).

Based on these prior results, we tested the hypothesis that a TAH rule, similar to the spike-time-dependent plasticity rule observed in experimental animal preparations, governs associative plasticity in the adult human motor cortex in vivo. We show that PAS may induce a depression of cortical excitability if the sequence of stimulation-induced events in the primary motor cortex is reversed within a small time window. Additional physiological properties of this form of plasticity suggest the involvement of associative LTD-like mechanisms. Some of the results have been published in abstract form (Sandbrink et al. 2001).

**METHODS**

**Subjects**

The study was approved by the Ethics committee of the University of Rostock and written informed consent was obtained from all participants. Experiments were performed on 34 healthy volunteers (19 men, 15 women) aged 18 to 44 yr (mean 27.8 ± 5.7 yr). None had a history of physical or neurological illness. All volunteers were right handed, except two, who were left handed, according to the Oldfield handedness inventory (Oldfield 1971).

**Stimulation**

Focal TMS was performed using a flat figure-eight-shaped magnetic coil (diameter of each wing: 70 mm) connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, Dyfed, UK). The coil was held tangentially to the skull with the handle pointing backward and laterally at a 45 deg angle to the sagittal plane.

Electrical mixed nerve stimulation was performed with an electrical stimulator (Type S88; Grass Instruments, West Warwick, Richmond, VA) connected to a stimulus isolation unit (SIU 8T; Grass Instruments) using a standard stimulation block (cathode proximal) at a stimulation width of 200 μs.

**Recording**

Electromyographic activity was recorded from the right APB muscle using disposable silver–silver chloride surface electrodes (Dantec Medical, Skovlunde, Denmark) in a belly-tendon montage. Raw signals were amplified employing a Toennies amplifier (Jaeger-Toennies, Würzburg, Germany) and band-pass filtered between 5 and 1500 Hz. Electromyographic (EMG) signals were digitized at 5 kHz by an A/D converter (model 1401 plus, Cambridge Electronics Design, Cambridge, UK) and stored in a laboratory computer for display and later off-line analysis.

**Experimental procedures**

Subjects were seated comfortably in an armchair. At first, the optimal position of the magnetic coil for eliciting MEP in the resting right APB was assessed over the left motor cortex at a moderately suprathreshold stimulation intensity (usually around 50% of the maximal stimulator output) and marked directly on the scalp with a soft-tip pen. At the optimal site, the resting motor threshold (RMT) was determined as the minimum stimulator intensity needed to produce a response of ≥50 μV in the relaxed APB in ≥5 of 10 consecutive trials (Rossini et al. 1994).

Complete muscle relaxation was continuously monitored by visual and auditory feedback. If not stated otherwise, 20 trials were collected both before and immediately after intervention, using a stimulus intensity of 1.3 times RMT and a stimulation rate of about 0.1 Hz. Previous studies (Stefan et al. 2000, 2002) had shown that this stimulation intensity evokes a mean MEP amplitude of the resting APB muscle averaging to approximately 1 mV in the resting APB. Identical stimulus intensities were used before and after intervention.

For intervention, a slightly modified version of a previously published PAS protocol (Stefan et al. 2000) was employed. In brief, the intervention consisted of single electrical stimuli delivered to the right median nerve at the level of the wrist at 300% of the perceptual threshold and followed by TMS at 1.3 times RMT at a fixed inter-stimulus interval (ISI). Ninety pairs were delivered at 0.05 Hz over 30 min.

**Timing of TMS pulse in relation to median nerve stimulation during intervention**

The influence of the timing of the TMS pulse with reference to the median nerve stimulation during PAS was studied in a total of 117 separate experimental sessions (13 experiments each at each of 9 ISIs). While all subjects were tested at multiple ISIs, not all of them were available for testing of all nine ISIs. Therefore to obtain data from the same number of subjects for each ISI, a total of 23 subjects was studied in this experiment. ISIs of −10, 0, 5, 10, 15, 20, 25, 35, 50 ms were tested and the interventions were termed [PAS(−10 ms), PAS(0 ms), · · · PAS(50 ms)], respectively, with positive values indicating that median nerve stimulation was followed by TMS. A schematic version of the experimental set-up is provided in Fig. 1A. At least 2 days elapsed in between two sessions for one subject. For each subject the order of the experimental sessions employing a specific ISI was pseudorandom. Effects of PAS on MEP amplitude were expressed as percentage difference (Δ%) compared with baseline MEP amplitudes.

**Somatosensory evoked potentials**

Somatosensory evoked potentials (SEP) were collected from a subgroup of 14 subjects participating in the experiment testing the effects of varying the ISIs (see paragraph above). Median-nerve SEP were recorded according to international guidelines (Niuwer et al. 1994) using needle electrodes. The active electrode was placed over the skull region overlaying the primary somatosensory cortex (C3 using the international 10–20 system) while the reference electrode was placed over Fz. For each of a minimum of three reproductions, 300 electrical stimuli (pulse width 300 μs, 5 Hz, 15–20 mA) were applied to the contralateral median nerve.

**F-wave studies and electrical brain stem stimulation**

As TMS-evoked MEPs are predominantly generated by activation of the monosynaptic corticospinal tract (Rothwell 1997), excitability changes following PAS(10 ms) could, in principle, be located at a cortical or a spinal level. To acquire information on the excitability of the spinal motor neurons uncontaminated by intracortical physiological changes, we employed F-wave studies and brain stem stimulation. Excitability of a portion of spinal motoneurones can be assessed by testing changes in the magnitude of F-waves, which are generated by a recurrent discharge of antidromically activated spinal motoneurones (Mayer and Feldman 1967). Transmastoïd stimulation in humans has
been shown to excite corticospinal axons at the level of the brain stem and evaluation of MEP amplitudes evoked by brain stem stimulation provides information on the excitability of spinal circuitry (Ugawa et al. 1991).

**F-wave studies**

In five subjects, changes in the MEP amplitudes following PAS were compared with changes in the size of F-waves evoked in the relaxed APB by supramaximal electrical stimulation of the median nerve at the wrist before and after PAS(10 ms). Twenty F-waves and 20 TMS-evoked MEP responses were recorded before and after intervention. The magnitude of F-waves depends on the intensity of the electric nerve stimulation eliciting it. The magnitude of N-waves elicited by peripheral nerve stimulation was compared before and after PAS as a surrogate marker of the peripheral efficacy of the electric median nerve stimuli delivered to elicit F-waves. In all experiments, M-wave amplitudes after PAS were within 95–105% of the preinterventional value, suggesting stability of peripheral nerve excitability.

**Brain stem stimulation**

In one subject electrical brain stem stimulation was performed using the method described by Ugawa and co-workers (1991). Anode (right) and cathode (left) were attached to the skin overlying the mastoids. Magnetic stimulation was performed at 1.3 times RMT. Stimulus intensity of the electric stimulator was then set to produce an MEP of similar amplitude in the resting APB. Stimulus intensity was the average of 20 recordings obtained before (pre) and after (post) interventional paired associative stimulation. Numbers on the left refer to the interstimulus interval used during paired associative stimulation. Right vertical bars represent calibrations bars (mV). C: group data (means ± SE). Asterisks indicate significant change of MEP amplitudes (P < 0.05). Vertical broken line indicates approximate time of arrival of afferent signal in the primary somatosensory cortex (Allison et al. 1989) as assessed by mean N1-response latency of the median-nerve somatosensory-evoked potential in 14 subjects (Nuwer et al. 1994).

**Pharmacological testing**

Most forms of LTD in neocortex depend on activation of N-methyl-D-aspartate (NMDA) receptors (Dodt et al. 1999; Kirkwood et al. 1999) and of L-type voltage-gated Ca²⁺ channels (Artola et al. 1996; Brocher et al. 1992; Dodt et al. 1999; Sjostrom and Nelson 2002). We tested the effects of dextromethorphan, an NMDA-receptor antagonist (Wong et al. 1988), and nimodipine, a blocker of L-type voltage-gated Ca²⁺ channels (Hess et al. 1984), on PAS(10 ms)-induced decrease of cortical excitability.

Twelve subjects were screened in an inclusion experiment. Eleven subjects fulfilled the inclusion criterion which specified that PAS(10 ms) must induce a depression of cortical excitability. These subjects were scheduled to participate in three subsequent sessions, separated by ≥2 days, in a single-blind, counterbalanced design. In one of the three sessions, each subject received a single dose of 150 mg dextromethorphan (Hustenstiller-Ratiopharm, Ratiopharm, Ulm, Germany); in another session, each subject received a single dose of 30 mg nimodipine (Nimotop S, Bayer, Leverkusen, Germany), and in a third session, each subject received a placebo. At the doses utilized in this study, dextromethorphan brain concentrations in humans (Steinberg et al. 1996) are similar to those that induce NMDA receptor block in vitro (Apland and Braimton 1990; Wong et al. 1988), and nimodipine concentrations in cerebrospinal fluid (Allen et al. 1983) are similar to those inducing blockade of LTD in vitro (Bi and Poo 1998).

Following each experimental session, side effects were graded by the subject on a scale ranging from 0 to 3 (0: no or very minor side effects; 1: minor side effects; 2: moderate side effects; 3: severe side effects). Of 11 subjects, 1 subject who received dextromethorphan in the first drug session experienced nausea shortly before the beginning of the first TMS investigation. This experimental session was discontinued and this subject was excluded from participation in further drug experiments.

For MEP amplitudes, 20 trials were collected both before and immediately after PAS(10 ms), using a stimulus intensity of 1.3 times RMT and a stimulation rate of 0.1 Hz. All analyses were done blind to the condition tested.

**Duration of PAS-induced depression of motor cortex excitability**

In 10 subjects the duration of the depression of motor cortex excitability elicited by PAS(10 ms) was studied. Twenty stimuli were delivered before PAS(10 ms), and at 10 epochs following PAS(10 ms), at 0, 10, 20, 30, 45, 60, 75, 90, 105, and 120 min.

![FIG. 1](http://jn.physiology.org/)

**A** principles of experimental design. Test amplitudes were elicited by single-pulse transcranial magnetic stimulation (TMS) before and after the intervention. During interventional stimulation, 90 pairs, consisting of electrical stimuli delivered to the right median nerve followed by TMS over the left hemisphere at the optimal site for activating the APB muscle, were applied using a constant interstimulus interval, at a frequency of 0.05 Hz. The interval between the 2 associative stimuli was varied in different sessions. **B** and **C**: effect of paired associative stimulation with interstimulus intervals of ~10–50 ms on motor-evoked potentials (MEP) size of the right APB. **B**: example of 1 subject. Each record shows the average of 20 recordings obtained before (pre) and after (post) interventional paired associative stimulation. Numbers on the left refer to the interstimulus interval used during paired associative stimulation. Right vertical bars represent calibrations bars (mV). C: group data (means ± SE). Asterisks indicate significant change of MEP amplitudes (P < 0.05). Vertical broken line indicates approximate time of arrival of afferent signal in the primary somatosensory cortex (Allison et al. 1989) as assessed by mean N1-response latency of the median-nerve somatosensory-evoked potential in 14 subjects (Nuwer et al. 1994).
Resting motor threshold to TMS provides information on membrane excitability levels (Hallett 2000; Mavroudakis et al. 1994; Ziemann et al. 1996). To consider this mechanism potentially contributing to PAS(10 ms)-induced depression of MEP amplitudes, RMT was assessed after intervention with PAS(10 ms) in four subjects.

Data analysis

Amplitudes were measured peak-to-peak in each individual trial. For each subject, amplitudes were averaged according to the different conditions described above and expressed as percentage of baseline. If not stated otherwise, analyses of variance (ANOVA) and post-hoc one-sample two-tailed t-test were employed for statistical analyses. Effects were considered significant if P < 0.05. All data are given as means ± SE.

RESULTS

Influence of interstimulus interval between peripheral and cortical stimulation

Following PAS, motor cortical excitability changed as a function of the ISI (f = 4.05, P < 0.001). Post-hoc analysis of the change of MEP amplitudes (Δ%) revealed significant effects for ISI = 25 ms and ISI = 10 ms. At 25-ms ISI, motor excitability increased by 51 ± 18% (P < 0.05), in agreement with previous observations (Stefan et al. 2000). At this ISI, MEP amplitudes increased in 11 of 13 subjects. On the other hand, at ISI = 10 ms motor excitability decreased by −25 ± 10% (range −7 to −85%, P < 0.05), and MEP amplitudes decreased in 11 of 13 subjects. An example of the effect of PAS performed with different ISIs is illustrated in Fig. 1B; group data are shown in Fig. 1C.

The latency of the N1 component (Nuwer et al. 1994) of the SEP after contralateral afferent median nerve stimulation remained constant (right bar). Asterisk indicates significant change of MEP amplitudes following PAS(10 ms) in 1 subject. Recordings show averages of 20 trials. Vertical broken lines indicate timing of the stimulation as shown by the stimulation artifact. Following paired associative stimulation at interstimulus interval (ISI) = 10 ms TMS-evoked MEP amplitudes decreased (top traces), whereas F-waves (bottom traces, insets) did not. M-wave responses (bottom traces) remained constant, suggesting stability of the efficacy of peripheral nerve stimulation. Number on the left of the lower calibration bar refers to M-waves; number on the right refers to the F-waves, as displayed in the inset. B: data from 5 subjects. Following PAS(10 ms), MEP amplitudes decreased in the APB (left bar), while the size of F-waves elicited in the APB remained constant (right bar). Asterisk indicates significant change of MEP amplitudes. C: comparison of TMS-evoked and brain stem stimulation-evoked MEP amplitudes modulated by PAS(10 ms) in 1 subject. Recordings show averages of 20 trials (TMS) or 6 trials (brain stem stimulation). Vertical broken lines indicate timing of the stimulation as shown by the stimulation artifact. Following interventional paired stimulation, TMS-evoked MEP amplitudes decreased (top traces), whereas brain stem stimulation-evoked MEP amplitudes (bottom traces) did not.

Physiological profile of PAS(10 ms)-induced depression of corticospinal excitability

Site on the neuroaxis

Two different approaches were used to examine the laminar site of the motor excitability changes: F-wave studies and transmastoid brain stem stimulation.

Following PAS(10 ms), the size of TMS-evoked MEPs decreased (−28 ± 6%, P < 0.01; n = 5), while the magnitude of F-waves elicited by median-nerve stimulation in the APB muscle remained unchanged (1 ± 6%; n.s., 1-sample, 2-tailed t-test; Fig. 2, A and B).

Following PAS(10 ms), MEP amplitudes to TMS decreased (mean ± SD; pre: 2.6 ± 1.5 mV, post: 1.5 ± 0.9 mV; P < 0.01; 2-sided t-test), while MEP amplitudes evoked by brain stem stimulation did not change significantly (pre: 2.0 ± 0.9 mV, post: 2.6 ± 1.2 mV; n.s.; Fig. 2C). These findings point to a cortical site underlying the depression of corticospinal excitability following PAS(10 ms).

Duration

Following PAS(10 ms), the duration of corticospinal excitability change varied with epoch (f = 2.44; P < 0.02). MEP amplitudes were depressed for approximately 90 min post intervention before returning back to the baseline level (Fig. 3).

Resting motor thresholds

Following PAS(10 ms), MEP amplitudes decreased (−29 ± 6%; P < 0.01; n = 4) in the absence of changes in resting motor thresholds [pre: 38 ± 9% of maximal stimulator output (MSO); post: 38 ± 9% of MSO], thus indicating that membrane excitability change is not a major mechanism contributing to the decrease of TMS-evoked MEP amplitudes.

Pharmacology

In the 10 subjects completing the pharmacological experiment, side effects (dizziness and nausea) were subjectively
graded 0.4 ± 0.7 (mean ± SD) in the dextromethorphan sessions, 0.0 ± 0.0 in the nimodipine sessions, and 0.0 ± 0.0 in the placebo sessions (n.s.; repeated measures ANOVA), respectively, and did not interfere with the subjects’ ability to complete the study. Motor cortical excitability changes induced by PAS(10 ms) were differentially influenced by the factor drug (F = 5.576, P < 0.005). PAS under the influence of placebo changed MEP amplitudes by -23 ± 8% (P < 0.05), similar to the magnitude of the decrease observed in the inclusion experiment (-24 ± 5%; P < 0.01; Fig. 4). Both dextromethorphan and nimodipine blocked PAS(10 ms)-induced excitability changes seen in the placebo session (Fig. 4).

**DISCUSSION**

The present results provide evidence that associative plasticity in the human motor cortex is governed by a strict temporally asymmetric rule. Following PAS(25 ms) motor cortex excitability increased, whereas PAS(10 ms) led to a depression of MEP amplitudes.

Afferent inputs elicited by median nerve stimulation reach the primary somatosensory cortex at the latency of the N1 component of the somatosensory-evoked potential (Allison et al. 1989), which amounted to 18.8 ± 0.3 ms in our subjects. Because, in humans, afferent inputs reach the primary motor cortex a maximum of 4 ms later than the primary somatosensory cortex (Goldring et al. 1970) (i.e., in our subjects, on average, at ±23 ms), the events triggered by TMS precede the events elicited by median nerve stimulation in the motor cortex at PAS(10 ms), whereas the sequence of events is reversed at PAS(25 ms). Our finding that bidirectional cortical excitability changes occurred with afferent stimulation-induced cortical events timed to fall within a few milliseconds before or after the postsynaptic events induced by TMS agrees with observations in several associative induction protocols in hippocampal (Debanne et al. 1998; Gustafsson et al. 1987; Hashemzadeh-Gargari et al. 1991; Huerta and Lisman 1995; Magee and Johnston 1997; Stanton and Sejnowski 1989) and in neocortical preparations (Markram et al. 1997). This temporal rule alone may indicate that similar cellular mechanisms may be involved. However, in the absence of invasive neuronal recordings any hypothesis about the precise nature or location of cellular events finally resulting in timing-dependent plasticity induced by our PAS protocol in human motor cortex remains speculative.

In the “classical” model of associative, “Hebbian” plasticity, the weak input to a postsynaptic neuron is strengthened when it is activated before activation of the postsynaptic neuron, whereas the opposite effect is induced when the sequence of events is reversed. In our paradigm, LTP(LTD)-like phenomena were obtained when TMS-induced events in the primary motor cortex followed (preceded) the events induced by peripheral stimulation. In the framework of the Hebbian model this would indicate that, during PAS, TMS has activated the
postsynaptic neuron. On the other hand, the response to TMS was enhanced or depressed after PAS, indicating that, following PAS, TMS has probed the PAS-induced modulation of the Hebbian model’s weak synapse. This apparent contradiction may be resolved by postulating similar spatial properties of the input specificity of Hebbian synapses in motor cortex as established in vitro, in organotypical slice cultures of rat hippocampus (Engert and Bonhoeffer 1997). It was shown that the efficacy of synapses undergoes modulations similar to those synapses altered by associative stimulation if they are located on the same postsynaptic neuron within a short distance (< 70 μm) of the latter. Assuming that synapses activated by TMS are located at a short distance from the synapse activated by afferent input, modulation of the amplitude of TMS-evoked MEPs could represent a “neighboring” effect from modulation of that synapse. An alternative hypothesis, favored by us, would be if the excitatory interneuron receiving afferent input would also be part of the chain of interneurons activated by TMS (Amassian et al. 1987; Ziemann and Rothwell 2000), for example, by recurrent collaterals. This latter model has similarities to one derived from behavioral experiments employing pairing of visual stimuli (Yao and Dan 2001).

The physiological properties of the PAS(25 ms)-induced increase of cortical excitability fulfill necessary criteria of LTP (Stefan et al. 2000, 2002). The present results have additionally revealed that the physiological profile of PAS(10 ms)-induced depression of motor cortical excitability is similar to that of LTD as elucidated in vitro studies (Bear and Malenka 1994; Malenka 1994; Malenka and Nicoll 1993): rapid evolution (within 30 min), persistence after the end of associative stimulation (lasting short of 2 h), reversibility (return to baseline at 120 min), dependence on activation of NMDA-receptors, and involvement of L-type voltage-gated Ca2+ channels. Therefore together our findings provide evidence that a TAH rule governs the induction of LTD/LTP-like phenomena in vivo in the human primary motor cortex.

Computational models have shown that a temporally asymmetric form of spike-time-dependent plasticity possesses significant advantages over a Hebbian plasticity that is based on correlation alone, as it leads to stable neuronal selectivities and cortical maps, while it accepts activity in both feedforward and feedback network connections without any additional constraints (Song and Abbott 2001). By demonstrating bidirectional modulation of cortical excitability in vivo, our findings may add weight to the concept of a TAH rule as a fundamental principle of operation of the brain with surprising general applicability including executive brain regions in the adult cortex. Recent studies in the visual cortex suggest important implications of such a rule on behavior. In the developing visual cortex of kittens repetitive pairing of a visual grating stimulus with an electrical stimulus delivered to the cortex induced a shift in orientation tuning of visual cortex neurons (Schuett et al. 2001). Evidence of a similar function in adult visual cortex was provided by findings that changes of orientation tuning followed pairings of two visual stimuli at two orientations (Fu et al. 2002; Yao and Dan 2001). Importantly, the direction of the shift depended on the temporal order of the stimuli and required interstimulus intervals of 40 ms or less (Yao and Dan 2001). The functional consequence of a TAH rule for motor plasticity is not a priori clear. The requirement of near-synchronicity by associative signals for modulation of cortical excitability would suggest that reafferent activity from peripheral mechanoreceptors induced by a voluntary movement would arrive too late in the primary motor cortex to provide a signal with which movement-related motor cortical neuronal activity could interact through the mechanism shown in the present paper, to effectively modulate the strength of synapses. However, it must be borne in mind that TMS recruits inhibitory circuits in addition to excitatory connections (Rothwell 1997). This might have narrowed the width of the time window for pre- and postsynaptic events to interact effectively. Therefore at the present time it cannot be excluded that reafferent mechanoreceptive signals may be able to influence efficacy of excitatory synapses within the motor cortex. However, it is important to note that any interaction of previously active cortical circuits with short-latency feedback from any (peripheral or cortical) reafferent signals will lead to depression of cortical excitability, thus supporting a role for LTD in information storage in the neocortex.

Previous investigators have utilized TMS to either induce cortical plasticity in the presence of manipulating afferent somatosensory information (e.g., Ziemann et al. 2002) or to test the hypothesis of a synaptic nature of practice-induced plasticity of cortical excitability (e.g., Bonato et al. 2002). These studies have revealed bidirectional changes of cortical excitability consistent with LTD or LTD of cortical synapses. Our study extends these previous findings by highlighting temporal requirements of bidirectional modulation of cortical excitability in an associative stimulation protocol. Additionally, our observations raise the possibility of manipulating human cortical excitability regionally in a purposeful way. Regional disturbance of cortical excitability is implicated in a number of neurological disorders such as certain movement disorders, pain, stroke, and epilepsy. PAS-induced changes of excitability, by design, are generated in the target cortex undergoing conjoint near-synchronous stimulation. Therefore modulation of locally disturbed cortical excitability by stimulation protocols based on associative principles governed by temporal rules would represent an important advantage over pharmacological interventions which cannot discriminate between intact and malfunctioning cortical regions. Animal studies as well as observations in humans suggest that associative stimulation protocols may in principle be effective in other neocortical regions.

The authors thank Prof. Heiko Luhmann for helpful comments on an earlier version of the manuscript.

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