Clinical Neurophysiology 114 (2003) 1265–1271

www.elsevier.com/locate/clinph

Frequency-dependent, bi-directional plasticity in motor cortex of human adults

Julia B. Pitcher*, Michael C. Ridding, Timothy S. Miles

Department of Physiology, The University of Adelaide, Adelaide, SA 5005, Australia

Accepted 17 March 2003

Abstract

Objective: To determine whether the plastic changes induced in human motor cortex by afferent stimulation depend on stimulus frequency.

Methods: Transcranial magnetic stimulation was used to examine changes in corticospinal excitability in 20 subjects before and after combined peripheral (motor point) and central stimulation. Peripheral stimuli were given as either low frequency (3 Hz) or high frequency (30 Hz) trains.

Results: Low frequency stimulation induced prolonged depression of corticospinal excitability, while high frequency stimulation induced prolonged facilitation. These effects persisted for approximately 40–50 min after stimulation ceased.

Conclusions: Corticospinal plasticity induced by dual peripheral and central stimulation is bi-directionally-modifiable in the adult human, with the direction of change being frequency-dependent.

Significance: Therapies using peripheral stimulation to alter human motor cortex excitability could be tailored to exploit the differential effects of stimulus frequency on the direction of the excitability change.

Keywords: Transcranial magnetic brain stimulation; Cortical plasticity; Human hand; Depression; Facilitation; Motor point stimulation

1. Introduction

Recent studies have demonstrated that changes in peripheral afferent input cause the adult human motor cortex to reorganise. This study examined the effect of the frequency of afferent stimulation on the nature of this plastic response.

A number of studies have used transcranial magnetic stimulation (TMS) to show that motor cortical excitability is changed by several experimental interventions, as well as in some pathological conditions. For example, amputation (Pascual-Leone et al., 1996; Elbert et al., 1997; Chen et al., 1998), ischaemic block (Brasil-Neto et al., 1993), and the learning of a motor skill (Kossut and Siucinska, 1998; Hund-Georgiadis and von Cramon, 1999) all induce rapid and enduring alterations in the excitability of cortico-motor projections to specific muscles.

Increases in motor cortical excitability can also be induced experimentally by electrical stimulation of peripheral nerves (Hambdy et al., 1998; Ridding et al., 2000; Charlton et al., 2003), or by combining nerve or muscle stimulation with low frequency TMS of the motor cortex (Stefan et al., 2000; McKay et al., 2002). Plastic changes have also been induced by repetitive TMS (rTMS). Depending on the rTMS parameters used, the excitability of the motor cortex can be either increased or decreased (Chen et al., 1997; Berardelli et al., 1998; Maeda et al., 2000a,b; Muellbacher et al., 2000; Modugno et al., 2001). Finally, prolonged focal depression of motor cortex excitability can be induced by strong voluntary contractions of wrist flexors (Brasil-Neto et al., 1993, 1994), elbow flexors (Taylor et al., 1996), ankle dorsiflexors (McKay et al., 1995) and intrinsic hand muscles (Pitcher and Miles, 2002).

Thus, facilitation or depression of human motor cortex excitability can be induced by different interventions or conditions. However, there is no clear explanation for why some types of inputs lead to facilitation and others to depression.

* Corresponding author. Tel.: +61-8-8303-6433; fax: +61-8-8303-3356.
E-mail address: julia.pitcher@adelaide.edu.au (J.B. Pitcher).

1388-2457/03/$30.00
doi:10.1016/S1388-2457(03)00092-0

Cooper et al. (1979) suggested a mechanism for the plasticity of stimulus selectivity in individual neurons. This model proposes that active synapses are facilitated when the total synaptic response (i.e. the combined effect of inhibitory and facilitatory inputs) exceeds a critical fixed value termed the modification threshold (θ_m), but are depressed when the total synaptic response is greater than zero but less than θ_m. That is, these synapses are bi-directionally modifiable. Dudek and Bear (1993) showed that such 'Cooper synapses' exist in the CA1 region of the adult rat hippocampus in vitro. Not only are these synapses bi-directionally modifiable, but the sign of their synaptic plasticity depends on the input frequency. High frequency inputs induce long-term potentiation (LTP) and low frequency inputs induce long-term depression (LTD), with little or no plastic change induced by frequencies below 0.1 Hz or around 10 Hz. Heynen et al. (1996) subsequently confirmed these findings in the rat hippocampus in vivo. Limited evidence suggests that these synapses may exist in human cortex (Chen et al., 1996). If present, the existence of such synapses in the motor cortex could explain why some interventions increase corticospinal excitability while others decrease it.

Our aim in the present study was to determine if the direction of motor evoked response amplitude change induced by the stimulation depended upon the frequency of stimulation. We hypothesised that higher frequency stimulation would induce an increase in corticospinal excitability, while low frequency afferent stimulation would reduce it. We employed a dual peripheral and central stimulation paradigm (Stefan et al., 2000; McKay et al., 2002), at two frequencies of peripheral stimulation. Preliminary results have been presented in abstract form elsewhere (Pitcher et al., 2001).

2. Methods

2.1. Subjects

Ten females and 10 males aged 18–54 years (25.5 ± 8.5 years) gave informed written consent to participate in the study. The experiments were approved by The University of Adelaide Committee on the Ethics of Human Experimentation and were performed in accordance with the Declaration of Helsinki. Subjects had no relevant medical history and all investigations were on the right hand, which was the preferred hand for all but one subject. One subject did not return to perform the high frequency protocol and another did not perform the low frequency protocol. Thirteen subjects were followed out for 10 min after each frequency of stimulation, while 6 subjects were followed out for 1 h.

Subjects sat in a reclining chair with the right hand and forearm supported. The surface electromyogram (EMG) of the right first dorsal interosseous (FDI – the test muscle) was recorded with one electrode placed over its belly and the other over the metacarpophalangeal joint. Electrodes were also placed 2 cm apart along the right flexor carpi ulnaris (FCU – the control muscle). The EMG was amplified in the bandwidth 20 Hz–1 kHz, sampled at 2.1 kHz with a laboratory interface (Cambridge Electronic Design 1401, Cambridge, UK), and analysed off-line.

2.2. Protocol

Subjects attended two experimental sessions not less than 10 days apart. Each session consisted of recording baseline resting motor evoked potentials (MEPs), followed by a 30 min period of dual stimulation at either 3 or 30 Hz, the order of which was randomised between subjects. Resting MEPs were recorded immediately after dual stimulation ceased and again 10 min later. In 6 subjects, MEPs were recorded every 10 min for 1 h following dual stimulation. Four of these subjects also performed a second 30 Hz protocol in which the number of stimuli was the same as for the 3 Hz protocol.

2.3. Motor evoked potentials

All MEPs were measured with the muscle at rest. TMS were applied with a Magstim 200 magnetic stimulator through a figure-of-8 stimulating coil (The Magstim Co., Dyfed, UK) at the optimum scalp site over the left hemisphere for evoking MEPs from the contralateral FDI. The coil was oriented approximately 45 degrees to the sagittal midline, so that the induced current flowed in a plane perpendicular to the estimated alignment of the central sulcus. Motor threshold was taken to be the lowest TMS intensity that evoked MEPs of at least 50 μV peak-to-peak amplitude in the resting FDI in 5 of 10 trials. To measure the MEP amplitude, 10 TMS trials at a stimulus intensity of 120% threshold were recorded and the MEPs averaged.

2.4. Dual stimulation

'Dual stimulation' was used to induce changes in the excitability of the motor cortex. This consisted of trains of afferent inputs paired with a single TMS (cf Stefan et al., 2000; McKay et al., 2002). The trains of afferent signals were produced by electrical stimulation delivered every 10 s to the motor point of FDI at either 3 Hz (two pulses per 660 ms train) or 30 Hz (20 pulses per 660 ms train) (S48 stimulator, Grass Stimulators, Quincy Mass., USA). Four subjects also underwent a second 30 Hz protocol in which the number of pulses given for the 30 min period was the same as for the 3 Hz protocol (i.e. two pulses per 660 ms train delivered at 30 Hz). Pulse duration was 100 μs. Each train was paired with a single TMS pulse, delivered 25 ms after the onset of the motor point stimulation train, at the optimal scalp site for FDI. The intensity of both the TMS and the motor point stimulation were just above motor

threshold so that, when delivered alone, each elicited a small visible twitch in FDI. Total stimulation time at a given frequency was 30 min.

2.5. Data analyses

The ensemble average of 10 consecutive MEPs was determined in each run and expressed relative to the control MEP (see Section 3 for rationale). The effects of various factors on the amplitude of the averaged MEPs were analysed using between- and within-factor repeated measures analysis of variance, with specific contrasts (ANOVA; SPSS® for Windows v.9.0.1, SPSS Inc., 1989–1999). The between-factors were Muscle (up to two levels: FDI and FCU). The within factors were Frequency (up to two levels: 3 and 30 Hz) and Time (up to 8 levels: control, immediately after dual stimulation period and every 10 min after dual stimulation period for 1 h). Where a factor had more than two levels, the pattern of response was assessed by polynomial contrasts. *Post-hoc* analyses were carried out using Bonferroni's comparison with corrections. Relationships between variables were assessed by computing Pearson's product-moment correlation coefficient. All comparisons and correlations were two-tailed. Statistical significance was assumed at $P \leq 0.05$.

3. Results

Unless specified, the results of all analyses include all subjects. No significant changes were seen in the amplitudes of FCU MEPs following dual stimulation.

3.1. Resting threshold

The resting threshold for FDI did not change within or between sessions. The control or baseline MEP, elicited at a stimulus intensity equivalent to 120% of resting threshold, did not differ between sessions (ANOVA; $F = 0.442$; $P = 0.52$; $N = 19$). However, resting threshold differed significantly between subjects (ANOVA; $F = 677.9$; $P \leq 0.0001$, $N = 20$). In addition, the amplitude of the control MEP differed markedly between subjects (ANOVA; $F = 17.1$; $P = 0.001$; $N = 19$) and this was significantly negatively correlated with the magnitude of the change induced by 30 Hz stimulation (Pearson's $r = -0.57$; $P = 0.01$; $N = 19$); i.e. the larger the control MEP, the smaller the facilitation following 30 Hz stimulation. We have recently shown that this is due to individual variability in motor cortex input-output characteristics (Pitcher et al., 2002). MEPs were normalised to the control MEP to account for this variability.

3.2. Low-frequency stimulation

Following 30 min of 3 Hz stimulation combined with TMS, the amplitude of FDI MEPs was depressed by 30.7 ± 14.8% (mean ± SEM) immediately following stimulation and remained depressed for at least 10 min after stimulation (Time; $F = 4.26$; $P = 0.02$, $N = 19$). Fig. 1A shows the responses of one representative subject in whom MEP depression occurred following 3 Hz stimulation, with MEP amplitude reduced by approximately 50% immediately following stimulation and by approximately 70% of baseline 10 min later. Fig. 2 shows the combined group MEP responses before and after the two different frequencies of stimulation.

3.3. High-frequency stimulation

The combined group MEP responses following 30 min of 30 Hz stimulation are shown by the open triangles in Fig. 2. In contrast to the effect of 3 Hz stimulation, MEP amplitude following 30 Hz stimulation was facilitated (Time, $F = 5.90$; $P = 0.006$, $N = 19$). MEP amplitude was facilitated 158.4 ± 71.1% immediately following stimulation, and 164.1 ± 48.5% 10 min later, compared with the pre-stimulation control MEP (100%). Fig. 1B shows the responses of the same subject shown in Fig. 1A to 30 Hz stimulation. Immediately following 30 min of 30 Hz stimulation, the MEP was facilitated so that its amplitude was 50% greater than the baseline MEP. This facilitation persisted when MEPs were recorded 10 min later. Fig. 3 shows that, when MEPs were recorded for 1 h after stimulation, MEP facilitation persisted for approximately 50 min in these subjects ($N = 6$).

3.4. Total pulse number versus frequency

Responses to stimulation were also compared for 3 and 30 Hz stimulation when the total number of peripheral stimuli was held constant (i.e. 372 pulses). Fig. 4 shows the group responses of the 4 subjects in which total pulse number was held constant for both frequencies. Matching the pulse number did not alter the frequency-dependence of the responses (Frequency; $P = 0.002$; $N = 4$): 30 Hz stimulation produced either facilitation or no change, while 3 Hz stimulation always produced depression (Frequency × Time; $P = 0.013$; $N = 4$).

4. Discussion

This study sought to determine whether the sign (depression or facilitation) of the changes in the excitability of the motor cortex that are induced by afferent input paired with TMS depends on the peripheral stimulation frequency. Low frequency (3 Hz) stimulation induced depression, and higher frequency (30 Hz) stimulation induced facilitation in the corticomotor projection to the target muscle (FDI) without changing the motor threshold, and with no changes being induced in the projection to a more proximal muscle

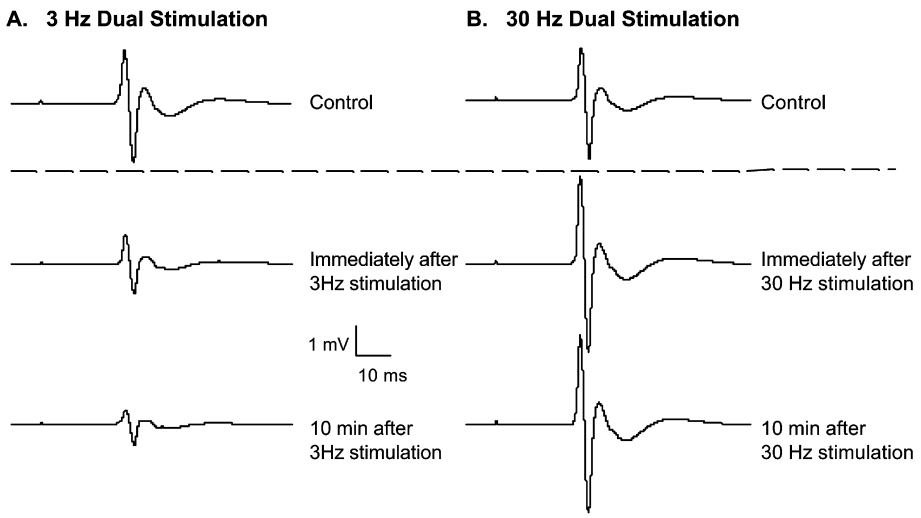

Fig. 1. Changes induced in MEPs evoked in FDI by TMS by high and low frequency motor point stimulation in one subject. Panel A: averaged MEPs elicited before and for 10 min following 30 min of 3 Hz stimulation. Low frequency stimulation typically induced depression of MEP amplitude that persisted for at least 10 min. Panel B: MEP responses before and 10 min following 30 min of 30 Hz stimulation. The 30 Hz stimulation facilitated MEP amplitude and this persisted for at least 10 min. Data are ensemble averages of 10 consecutive MEPs from the same subject.

(FCU). This occurred whether the total number of peripheral stimuli were the same or different (the same number and frequency of TMS were given in each protocol), indicating that the direction of the change is frequency-dependent.

These changes are therefore qualitatively similar to those induced by stimulation over the motor cortex with trains of TMS (rTMS), which also modulate cortical excitability in a frequency-dependent manner. Low frequency (0.9–1 Hz) rTMS induces MEP depression (Chen et al., 1997; Tergau et al., 1997; Maeda et al., 2000a,b; Muellbacher et al., 2000) while rTMS at higher frequencies (approximately 5–25 Hz) facilitates MEPs (Pascual-Leone et al., 1994; Berardelli et al., 1998; Maeda et al., 2000a,b). There is evidence that this rTMS-induced reorganisation occurs in the motor cortex (Wasserman et al., 1996; Berardelli et al., 1998; Modugno et al., 2001).

4.1. Bi-directional plasticity?

While we do not claim to have demonstrated the existence of bi-directional synapses in the motor cortex, a

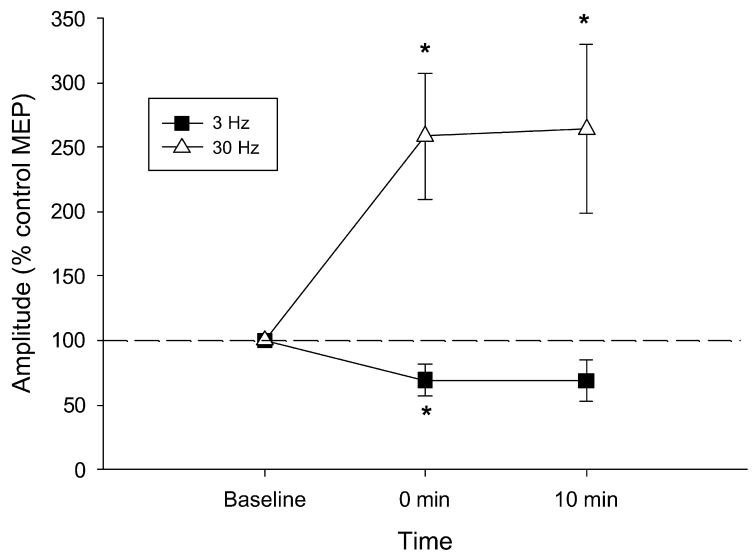

Fig. 2. Grouped data showing the pattern of stimulus-induced facilitation and depression of MEPs in FDI in the two experimental sessions. The open triangles show that 30-Hz stimulation of FDI motor point induced facilitation of corticospinal excitability in one experimental session. The filled squares show that 3 Hz stimulation induced depression of corticospinal excitability on a different occasion. Data are group mean ensemble averages of 10 consecutive MEPs (% control MEP) ± SEM. The asterisks denote $P \leq 0.05$ when compare to the control MEP (i.e. prior to dual stimulation). $N = 20$.

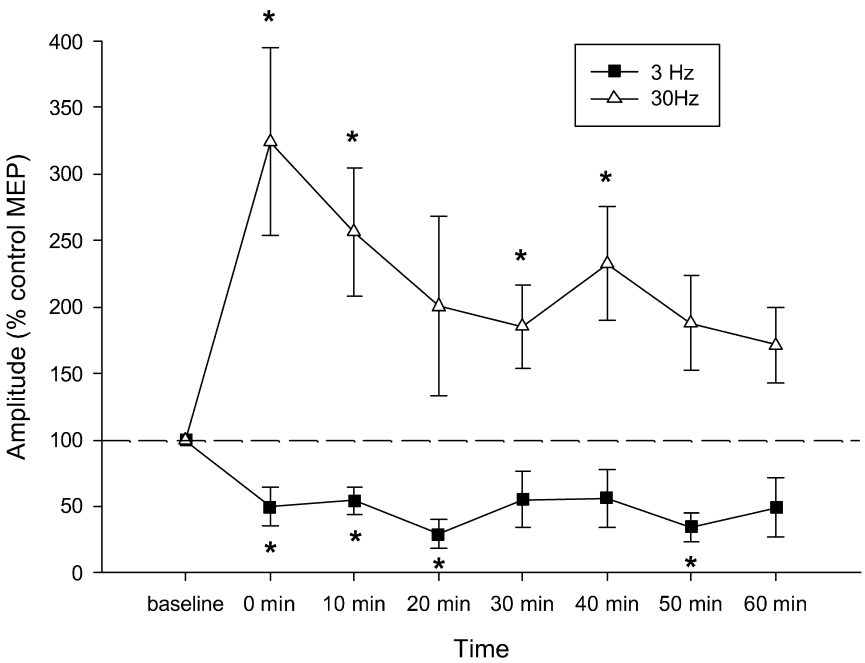

Fig. 3. MEP amplitude recorded in 6 subjects whose responses were followed out for 1 h. Following 30-Hz stimulation on one occasion, MEPs remained significantly facilitated for approximately 40 min (triangles). MEPs were depressed for approximately 50 min following 3-Hz stimulation (squares) in a separate recording session. Data are group mean MEP amplitude (% control MEP) ± SEM. $N = 6$.

number of characteristics of the cortical reorganisation described in this study are in accord with the hippocampal bi-directional plasticity described by Heynen et al. (1996), who showed that LTP and LTD are reversible modifications of the same Schaffer collateral synapses in the rat hippocampus in vivo. Low frequency (1–3 Hz) stimulation induced LTD while high frequency stimulation induced LTP, and these changes were specific to the synapses whose inputs had been stimulated. The rapid onset of the plastic changes in the current study suggests that the most likely mechanism is either strengthening (LTP) or weakening (LTD) of synaptic connections in a frequency-dependent manner.

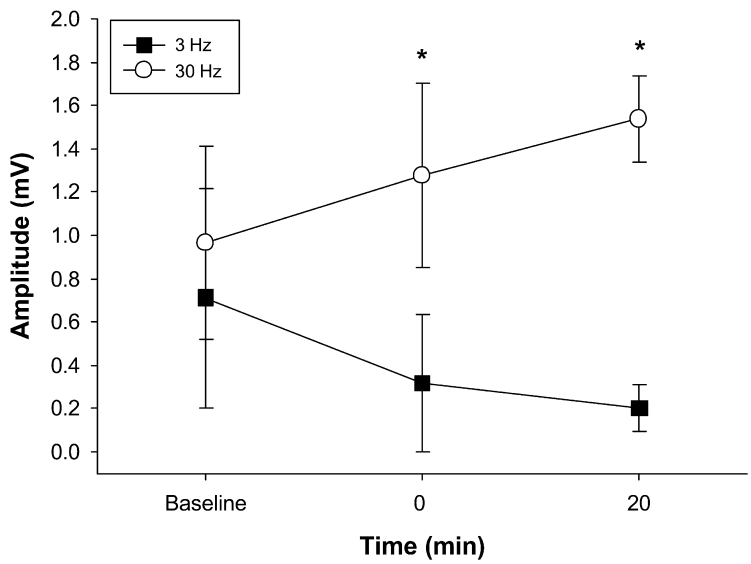

Fig. 4. Facilitation and depression of cortical excitability when the same total number of pulses was given in the 30-Hz protocol and the 3-Hz protocol in a subset of 4 of the original subjects tested. The same general pattern of excitability change was seen as in Fig. 2. That is, the direction of the change was still seen to depend on the stimulus frequency. In this protocol, 30-Hz stimulation induced either facilitation or no change in MEP amplitude, and 3-Hz stimulation induced depression in MEP amplitude in all subjects tested. Data are group mean MEP amplitudes (mV) ± SD. Asterisks denote $P \leq 0.05$ when the response amplitudes for each frequency are compared at a given time point.

The input specificity of motor cortex plasticity has been demonstrated in a series of animal studies by Asanuma and colleagues (reviewed in Asanuma and Pavlides, 1997). Neurons in the sensory cortex were stimulated (100 Hz for 20 s) and the synaptic potentials recorded in the motor cortex. Only those cells receiving direct input from the stimulated sensory cortex neurons were altered. In the current study, only the excitability of the projection to the target muscle (FDI) was altered.

The functional significance of bi-directionally-modifiable synapses is that it enables neurons to increase their stimulus selectivity, that is, to respond differently to different *patterns* of inputs (Bear, 1996). Synapses capable of experience-dependent bi-directional plasticity have been documented in the rat hippocampus, rat neocortex (Dudek and Bear, 1993; Markram et al., 1995; Markram and Sakmann, 1995; Heynen et al., 1996), mouse and cat visual cortex (Bear, 1996), rat visual cortex (Artola et al., 1990; Kirkwood et al., 1996), rat somatosensory cortex (Castro-Alamancos et al., 1995), rat sensorimotor cortex (Froc et al., 2000), and guinea pig visual cortex (Frégnac et al., 1994). They have also been demonstrated in human temporal cortex slices (Chen et al., 1996). However, it is not possible to know whether the frequency-dependent plasticity in the present study reflects true bi-directional plasticity at a given set of synapses, or frequency-driven predominance of either intrinsically inhibitory synapses or excitatory synapses in determining overall excitability.

This study shows not only that the plastic changes of corticospinal output induced by peripheral stimulation are bi-directionally-modifiable in the adult human, but also that they are frequency-dependent. The plasticity is qualitatively similar to bi-directional plasticity previously described in the hippocampus and to that evoked in humans with rTMS, and is most likely due to frequency-dependent strengthening and/or weakening of existing synapses in an input-specific manner.

Acknowledgements

We thank Dr Darrin McKay, Ms Joanna Lazarski and Dr Sophie Pearce for assistance with some of the experiments. JBP is an Australian Postgraduate Research Scholar. MCR is an Australian Research Council QEII Research Fellow. The Australian Research Council supported this work.

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