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RESEARCH ARTICLE

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Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects

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Abstract The aim of this study was to determine whether prolonged, repetitive mixed nerve stimulation (duty cycle 1 s, 500 ms on–500 ms off, 10 Hz) of the ulnar nerve leads to a change in excitability of primary motor cortex in normal human subjects. Motor-evoked potentials (MEPs) generated in three intrinsic hand muscles [abductor digiti minimi (ADM), first dorsal interosseous (FDI) and abductor pollicis brevis (APB)] by focal transcranial magnetic stimulation were recorded during complete relaxation before and after a period of prolonged repetitive ulnar nerve stimulation at the wrist. Transcranial magnetic stimuli were applied at seven scalp sites separated by 1 cm: the optimal scalp site for eliciting MEPs in the target muscle (FDI), three sites medial to the optimal site and three sites lateral to the optimal stimulation site. The area of the MEPs evoked in the ulnar- (FDI, ADM) but not the median-innervated (APB) muscles was increased after prolonged ulnar nerve stimulation. Centre of gravity measures demonstrated that there was no significant difference in the distribution of cortical excitability after the peripheral stimulation. F-wave responses in the intrinsic hand muscles were not altered after prolonged ulnar nerve stimulation, suggesting that the changes in MEP areas were not the result of stimulus-induced increases in the excitability of spinal motoneurones. Control experiments employing transcranial electric stimulation provided no evidence for a spinal origin for the excitability changes. These results demonstrate that in normal human subjects the excitability of the cortical projection to hand muscles can be altered in a manner determined by the peripheral stimulus applied.

Key words Magnetic stimulation · Motor cortex · Plasticity · Motor control

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Introduction

The organisation of primary sensorimotor cortex is responsive to peripheral and central manipulation by mechanisms that are important for learning motor tasks. The mechanisms that underlie this sensorimotor cortical plasticity are not well understood, but there is evidence that modulation of afferent inputs may play a central role, as demonstrated in experiments examining the effects of digital amputation (Calford and Tweedale 1988), peripheral nerve stimulation (Recanzone et al. 1990) or use dependency (Brons and Woody 1980; Nudo et al. 1996).

Behavioural training can also induce organisational changes in the cortex. Intensive training of monkeys with a skilled hand task over a period of months resulted in alterations in the organisation of the sensory cortex (Byl et al. 1996). These alterations included increases in the size of receptive fields of single cells by 10 to 20 times, and breakdown of the normally sharply segregated area 3b representations of volar glabrous and dorsal hairy skin of the hand (Byl et al. 1996). These and other authors (Clark et al. 1988) concluded that specific patterns of afferent activation consisting of coincident inputs from several peripheral zones are capable of producing reliable and lasting change within the monkey sensory cortex. Similar changes in the organisation of the primary motor cortex have been demonstrated after peripheral nerve lesions (Donoghue et al. 1990). The results of these studies and others (Nudo et al. 1996) have shown that primary motor cortex, like somatosensory cortex, is dynamically altered by behavioural experience.

Similar alterations in cortical organisation after changes in afferent input can be inferred in man from experiments using transcranial magnetic stimulation. An indication of the excitability of the corticospinal projection to a muscle can be obtained by mapping the scalp area from which responses in that muscle are evoked (e.g. Wilson et al. 1993) and it has been proposed that these changes may represent alterations in cortical organisation. The technique of transcranial magnetic stimulation mapping has been used to demonstrate that the excitability of the corticospinal projection is increased for muscles proximal to an amputation (Hall et al. 1990; Cohen et al. 1991; Ridding and Rothwell 1995) or nerve block (Brasil-Neto et al. 1993). Changes in cortical organisation consisting of an increase in the area of cortex activated during performance of a learned task are also evident on functional magnetic resonance imaging after acquisition of a new motor skill (Karni et al. 1995).

Therefore, the evidence is compelling for a major role of afferent input in influencing cortical organisation. The experiments described here were designed to investigate whether stimulation of peripheral nerves in a standardised manner could induce specific excitability and, by inference, organisational change in the human primary motor cortex.

Materials and methods

A total of ten normal subjects aged from 23 to 50 years (3 males and 7 female subjects) were studied. The protocols had ethical approval from the Human Research Ethics Committee of the University of Adelaide. Informed, written consent was obtained from all subjects. Surface electromyographic (EMG) activity was recorded from bipolar silver–silver chloride electrodes placed over abductor digiti minimi (ADM), first dorsal interosseous (FDI) and abductor pollicis brevis (APB) in the non-dominant hand. The active electrode was placed over the mid-point of each muscle and the reference electrode over the adjacent first interphalangeal joint. EMG responses were amplified (typically ×1000), filtered (20 Hz–5 kHz) and collected on a computer using a CED 1401 laboratory interface (CED, Cambridge, UK) for off-line analysis.

Mapping of cortical excitability

Six subjects underwent transcranial magnetic stimulation mapping. Stimulation was performed using a Magstim 200 magnetic stimulator (MAGSTIM Co. Ltd, Whitland, Dyfed, UK) and a figure-of-eight focal coil (10 cm external wing diameter). The optimal scalp site (site 4) for eliciting MEPs in the target muscle (FDI) was marked. In addition, three sites were marked medial and three sites lateral to the optimal scalp stimulation site in 1 cm steps (Fig. 1). Threshold was defined as the lowest stimulus intensity that produced five MEPs (minimum amplitude of 50 μV) in the relaxed FDI from ten stimuli applied to the optimal scalp site. Each scalp site was then stimulated with five stimuli at an intensity 20% above the threshold for evoking responses in the FDI, and the MEPs evoked in the three muscles were recorded and averaged. This procedure was repeated to ensure that the data were reproducible. Prolonged repetitive ulnar nerve stimulation was then initiated. When the period of repetitive peripheral nerve stimulation was terminated the mapping procedure was repeated.

Centre of gravity of cortical MEP maps

In order to identify shifts in muscle representations the centre of gravity (CoG) for each muscle was calculated before and after repetitive peripheral stimulation. The MEP amplitudes at each of the seven scalp sites were weighted using the distance of that site from site 4. The weightings were negative for sites medial to site 4 and positive for sites lateral to site 4. These calculations gave an indication of whether the CoG of the representational map for each muscle moved in a medial or lateral direction after the repetitive nerve stimulation. For each map the CoG was calculated using the following formula

$$X_{\mathrm{CoG}}=\sum a_i x_{i/}\sum a_i$$

where a_i is the mean amplitude measured at the scalp site whose coordinate is x_i.

Analysis

A two-way repeated-measures analysis of variance (ANOVA) was used to determine and compare the effect of ulnar nerve stimulation on the CoG of the three muscles studied. The factors were treatment (two levels: pre and post nerve stimulation) and muscle (three levels: FDI, ADM, APB) and their interaction. The significance level was set at $P<0.05$ and post-hoc analyses were performed where appropriate.

Repetitive ulnar nerve stimulation

Stimulus parameters were determined by preliminary experiments in which it was found that a period of mixed nerve stimulation lasting at least 1.5 hours was necessary to produce reliable and significant increases in the size of MEPs evoked in small hand muscles. Electrical stimuli (Grass S48) were delivered to the ulnar nerve at the wrist via surface electrodes (cathode proximal) in trains of 1 ms duration square-wave pulses at a frequency of 10 Hz, applied for 500 ms and then switched off for 500 ms. The stimulus intensity was adjusted to give a visible contraction of ulnar-innervated hand muscles. Subjects were instructed to refrain from moving the stimulated forearm and hand during the experimental procedure. After stimulation for 2 h the threshold for evoking MEPs was measured again and the mapping procedure repeated. To obtain an indication of the persistence of any changes produced by the repetitive mixed nerve stimulation, a further mapping period was undertaken in three subjects, 15 min after the cessation of repetitive ulnar nerve stimulation.

The effect of cutaneous input

In a separate series of experiments the effect of cutaneous input on cortical excitability was investigated in four subjects who had participated in the main series of experiments. To obtain baseline measurements mapping was performed as in the main series of experiments. The same repetitive nerve stimulus paradigm used in the main series of experiments was employed to stimulate the digital nerves of fingers 4 and 5. Stimulus intensity was adjusted to be approximately 2.5–3 times perceptual threshold. This resulted in a stimulus of similar intensity (relative to perceptual threshold) to that employed for the mixed nerve stimulation. All subjects readily tolerated this intensity of stimulation. The threshold for evoking MEPs was measured again and the mapping procedure repeated after stimulation for 2 h.

Analysis

The mean amplitude and area of MEPs in each muscle after magnetic brain stimulation was calculated for each stimulus site. Anal-

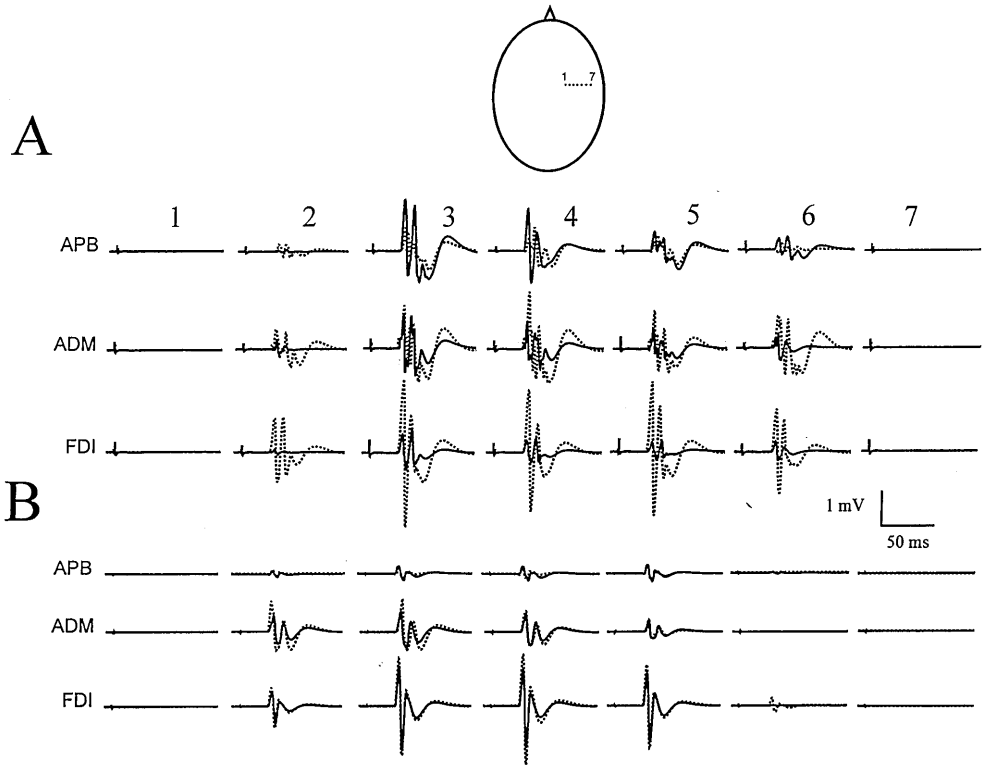

Fig. 1 Raw data traces from two representative subjects (**A**,**B**) showing the effect of a 2-h period of repetitive ulnar nerve stimulation at the wrist (10 Hz, 500 ms on/500 ms off) on the motor-evoked potential (MEP) amplitudes in three hand muscles. For each subject the pre-stimulation (*solid lines*) and post-stimulation (*dotted lines*) trials are superimposed. Each pair of traces represents stimulation at one scalp site (*1–7*). Each trace is the average of five responses. For both subjects, responses in first dorsal interosseous (FDI) and abductor digiti minimi (ADM) (both innervated by the ulnar nerve) are larger in the post-stimulus trials. Responses in abductor pollicis brevis (APB) (innervated by the median nerve) are not significantly different after the stimulation period

ysis of the results showed that area and amplitude measures gave very similar results. As several of the subjects investigated had moderately complex MEPs, measures of area are used throughout the paper. A three-way repeated-measures ANOVA was used to determine and compare the effect of ulnar nerve stimulation on the mean MEP area of the three muscles studied. The factors were treatment (two levels: pre and post nerve stimulation), site of stimulation (seven levels), muscle (three levels: FDI, ADM, APB) and their interaction. The significance level was set at $P<0.05$ and post-hoc analyses were performed where appropriate. Changes in the threshold and onset latency for MEPs after magnetic brain stimulation were analysed using paired *t*-tests. A similar analysis was used on the data obtained in the digital nerve stimulation experiments.

Level of excitability change

In order to provide evidence for the cortical nature of any observed change in corticospinal excitability, a further series of experiments was performed in five subjects. In these experiments MEPs were recorded in the right FDI using techniques described above. MEPs were evoked in a number of different ways. Firstly, with the subjects relaxed transcranial magnetic stimulation (TMS) was applied at 120% of relaxed threshold at the optimal scalp site for evoking responses in FDI. In a second trial, recordings were taken during a minimal voluntary contraction (approximately 5% of maximum voluntary contraction) and MEPs were evoked using both TMS and transcranial electrical stimulation (TES). In this second trial TMS and TES were presented pseudo-randomly to the subject, with trials consisting of five TES and ten TMS stimuli. Both the TMS and TES intensities were adjusted so that the amplitudes of evoked MEPs were matched with those elicited by TMS in the relaxed condition. TES was applied using a Magstim D180 stimulator. Silver–silver chloride cup electrodes (9 mm diameter) were used as stimulating electrodes. The anode was placed over the left motor cortex hand area (6 cm lateral to the vertex) and the cathode was placed at the vertex.

Analysis

A two-way repeated measures ANOVA was used to compare the effect of repetitive ulnar nerve stimulation on the MEPs evoked in FDI with the three forms of stimulation. The factors were stimulation type (three levels: TMS relaxed, TMS active, TES active) and treatment (two levels: pre- and post-stimulation).

F-wave studies

In six subjects (three of whom had participated in the mapping study) the excitability of spinal motoneurones after 2 h of ulnar nerve stimulation was investigated by recording F-waves. MEPs and F-waves were recorded from the left FDI muscle as this muscle showed the most dramatic MEP facilitation after the 2-h period of nerve stimulation. The optimal scalp site and threshold for evoking MEPs in FDI was determined as before and MEPs were measured after stimulation at this site only. F-waves were evoked by supra-threshold electrical stimulation of the ulnar nerve at the wrist. Twenty ulnar nerve stimuli and ten magnetic brain stimuli were presented in random sequence. MEPs and F-waves were recorded before and immediately after a 2-h period of repetitive ulnar nerve stimulation (as above) and the following measurements were made: 1) average MEP amplitude; 2) F-wave incidence (number of F-wave occurrences after 20 stimuli); 3) the average F-wave amplitude; and 4) average F-wave area. Paired *t*-tests were used to determine whether there was significant change in any of these measures after nerve stimulation.

Results

All subjects completed the protocol. None of the subjects reported any persistent complaint of weakness or paraesthesia after the prolonged stimulus. Although not tested systematically there was no obvious difference in

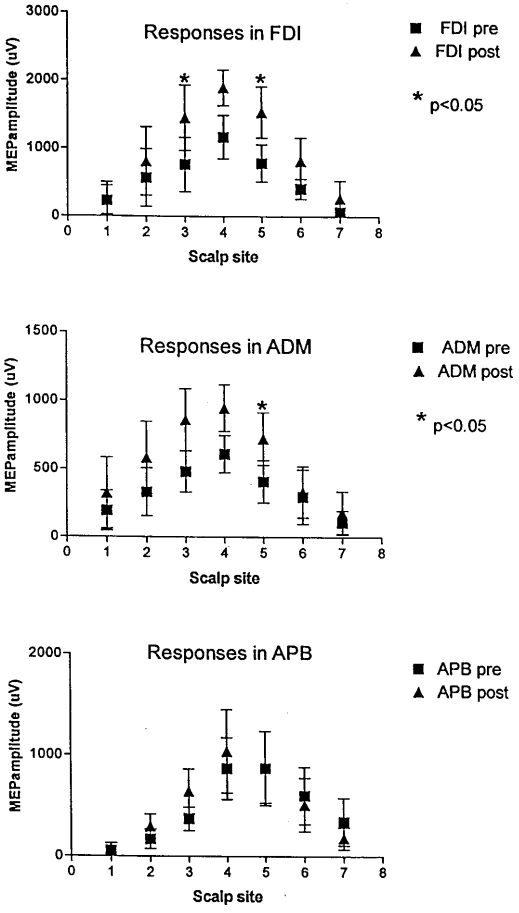

Fig. 2 Group data from six subjects showing the effect of peripheral nerve stimulation on the MEP areas in FDI, ADM and APB after stimulation at each of the seven scalp sites. Each point is the mean (±SE) of the data from six subjects, and each value for each subject is the average of ten responses. Scalp sites are shown on the horizontal axis and MEP amplitudes on the vertical axis. Responses from both FDI and ADM are significantly (ANOVA, $P<0.05$) larger after the period of ulnar nerve stimulation than those evoked in the baseline, pre-ulnar nerve stimulation condition. The increase in response amplitude is most apparent at sites close to site 4, the optimal scalp site for eliciting MEPs in FDI. Response amplitudes in APB were not significantly (ANOVA, $P>0.05$) affected by the period of ulnar nerve stimulation

sensory thresholds after the period of peripheral stimulation.

The threshold stimulus intensity required to evoke MEPs in the relaxed FDI with magnetic brain stimulation varied across subjects but was consistent throughout the duration of the experiment. The pre-stimulation threshold was 38.7±9.4% maximal stimulator output (mean±SD), which was not significantly different from the post-stimulation threshold of 38.3±8.9% ($P>0.05$). There was no significant difference in the onset latency of the MEPs evoked in the pre- and post-peripheral stimulation conditions (paired *t*-test, $P>0.05$ for all three muscles). For FDI, the pre-stimulation MEP onset latency was 22.7±1.8 ms (mean±SD) and post-stimulation 22.5±1.7 ms; for ADM, pre 22.0±2.1 and post 21.8± 1.8 ms; for APB, pre 22.0±1.8 and post 21.9±1.8 ms.

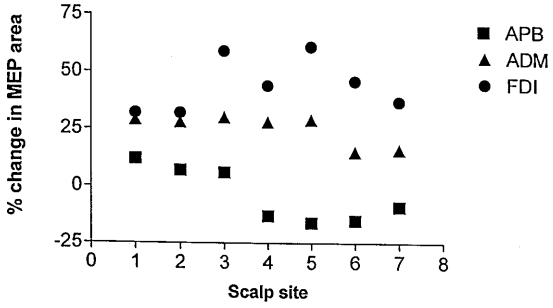

Fig. 3 Average percentage change in MEP area for the three muscles investigated. At each scalp site (*1–7*) the average percentage change in MEP area after the 2-h period of peripheral nerve stimulation is shown for the six subjects investigated. It can be seen that FDI and ADM have greater increases (ANOVA, $P<0.05$) in MEP area than APB

Mapping studies of MEP area

Response amplitudes from the two mapping trials conducted before the period of repetitive ulnar nerve stimulation were highly correlated ($r=0.85$, $P<0.05$), and, therefore, were combined for further analysis. Similarly, the two mapping trials conducted after the period of repetitive ulnar stimulation were also correlated ($r=0.82$, $P<0.05$) and, therefore, were combined for analysis. Examples of MEPs evoked in the three muscles from the seven scalp sites before and after ulnar nerve stimulation are shown for two representative subjects in Fig. 1.

When the effect of repetitive ulnar nerve stimulation across all three muscles investigated was examined it was found that repetitive stimulation significantly changed MEP areas (ANOVA, $P<0.05$). The change in MEP area varied with muscle (ANOVA, muscle–treatment interaction, $P<0.05$; see Fig. 1). This indicates that not all the muscles behaved in a similar way after the repetitive ulnar nerve stimulation.

Post-hoc analysis confirmed that significantly larger MEPs were generated post repetitive nerve stimulation in the ulnar-innervated FDI ($P<0.05$) and ADM ($P<0.05$) muscles, but not in APB ($P>0.05$). There was a significant interaction effect of treatment–muscle when FDI and APB ($P<0.05$) or ADM and APB ($P<0.05$), but not ADM and FDI ($P>0.05$), were compared. These findings indicate that FDI and ADM behaved similarly to each other but in a significantly different manner to APB. In FDI and ADM, increases in amplitude were evident across all sites. The group data are summarised in Fig. 2, in which the optimal scalp site for stimulation is site 4.

The percentage change in MEP area at each scalp site and for each muscle is shown in Fig. 3. There is a consistent increase in MEP area across all seven stimulation sites for ADM. In APB there is a small increase in the area of MEPs at medial sites and a decrease in the area of MEPs at central and lateral sites. In FDI, medial stimulation sites show a moderate increase in MEP area, with larger increases in MEP areas at central and lateral sites.

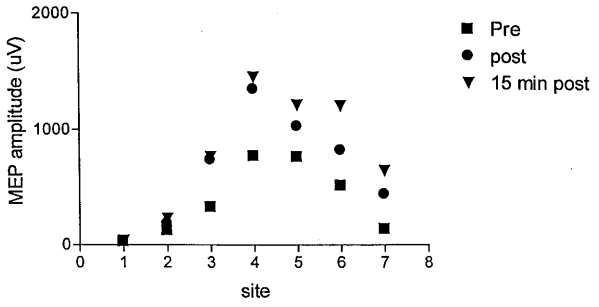

Fig. 4 Amplitudes of MEPs evoked in FDI for three subjects, at the seven scalp sites, are shown. Each point is an average of the data from the three subjects. The individual values obtained for each subject were the average of ten responses after transcranial magnetic stimulation (TMS) at 120% of relaxed threshold. After the 2-h period of ulnar nerve stimulation there is a significant increase in response amplitude (ANOVA, $P<0.05$). This increase in amplitude is still present when measurements were repeated 15 min after the end of the nerve stimulation period

The increase in MEP area at more lateral sites in FDI has a similar distribution to the decrease in APB MEP areas.

The increase in MEP area seen in ADM and FDI after the repetitive stimulation was still evident when measurements were taken 15 min after cessation of peripheral nerve stimulation in the three subjects tested (Fig. 4).

Centre of gravity

There was no significant difference (ANOVA, $P>0.05$) in the CoG for any of the three muscles investigated after the repetitive peripheral nerve stimulation (see Table 1). The CoGs of the three muscles were: FDI pre-stimulation 0.14±0.85 cm (mean±SD), post-stimulation 0.21±0.81 cm; ADM pre –0.07±0.93 cm, post –0.13±1.00 cm; APB pre 0.39±0.87 cm, post 0.22±0.77 cm. These values are relative to site 4. CoGs medial to site 4 are negative and CoGs lateral to site 4 are positive.

Effects of cutaneous stimulation

In the four subjects investigated, 2 h of repetitive digit 4/5 stimulation did not significantly increase the size of MEPs when averaged across the same three muscles (ANOVA, $P>0.05$). All three muscles investigated behaved in a similar manner after the repetitive digital stimulation (ANOVA, muscle–treatment interaction, $P>0.05$).

Level of excitability change

In the baseline condition (pre-repetitive stimulation) the test response amplitudes were well matched under the three different brain stimulation conditions [TMS rest 0.73±0.19 mV (mean±SD); TMS active 0.93±0.27 mV; TES active 0.94±0.33 mV; ANOVA, $P>0.05$]. The repetitive peripheral nerve stimulation had a significant effect on the amplitude of the MEPs averaged across all three conditions (ANOVA, $P<0.05$; see Fig. 5). However, there was a significant interaction between stimulation type and treatment (ANOVA, stimulation–treatment $P<0.05$). This demonstrates that the MEPs evoked under the three different stimulation conditions behaved differently after the repetitive nerve stimulation. Post-hoc analysis revealed that after the repetitive nerve stimulation there was a significant increase in the amplitude of the MEPs evoked by TMS in the relaxed condition (2.16±0.51 mV, $P<0.05$) but not with either TMS during voluntary contraction (0.98±0.21 mV, $P>0.05$) or TES during voluntary contraction (0.78±0.29 mV, $P= 0.21$).

F-wave studies

F-waves were recorded from FDI in six subjects before and after peripheral nerve stimulation. MEPs were also recorded during this series of experiments (see Materials and methods). In these subjects, the mean amplitude of the MEPs evoked by stimulation over the optimal scalp site increased from 0.99±0.42 mV (mean±SE) before stimulation, to 2.16±0.77 mV after stimulation ($P<0.05$). This increase in MEP amplitude was consistent with that seen in the earlier mapping experiments. There was no significant difference in M-wave amplitude in response to ulnar nerve stimulation in FDI (pre 9.56±0.93 mV, mean±SE, post 10.81±1.15 mV; paired *t*-test $P>0.05$) or ADM (pre 5.87±1.19 mV, post 5.72±1.34 mV; paired

Table 1 Centres of gravity (CoG) (relative to scalp site 4: the optimal scalp site for eliciting responses in FDI) for each of the three muscles in each subject before and after a 2-h period of repetitive ulnar nerve stimulation. *FDI* first dorsal interosseous, *ADM* abductor digiti minimi, *APB* abductor pollicis brevis

Subject	CoG (cm from scalp site 4; medial negative, lateral positive)					
	FDI		ADM		APB	
	Pre	Post	Pre	Post	Pre	Post
1	0.63	0.53	0.42	0.39	0.71	0.47
2	–0.18	0.49	0.04	0.15	–0.05	0.40
3	1.21	1.23	1.22	1.18	1.46	1.15
4	0.36	0.29	–0.25	–0.32	0.42	–0.09
5	–1.29	–1.20	–1.61	–1.83	–1.06	–1.12
6	0.13	–0.06	–0.28	–0.33	0.85	0.53
Mean±SD	0.14±0.85	0.21±0.81	–0.8±0.93	–13±1.00	0.39±0.87	0.22±0.77

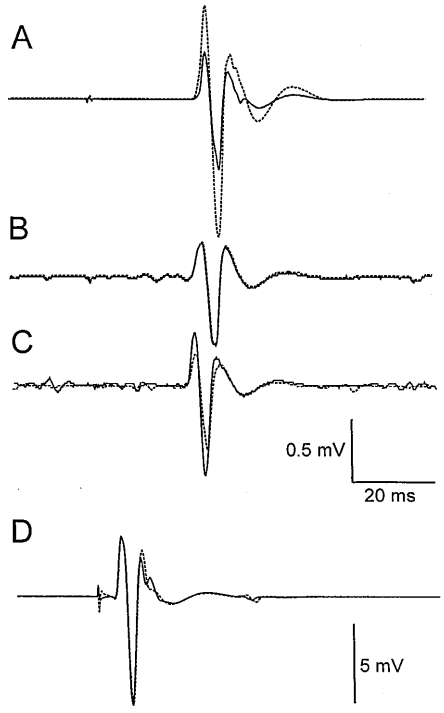

Fig. 5 Raw data from a representative subject during a control experiment where transcranial brain stimulation was applied under three different conditions before (*solid traces*) and after (*dotted traces*) a 2-h period of repetitive ulnar nerve stimulation. The top two superimposed traces (**A**) show the responses after TMS with the target muscle (FDI) relaxed. There is a clear facilitation of the MEP after the period of repetitive nerve stimulation. **B** shows responses to TMS during a small voluntary contraction and **C** shows the responses to transcranial electrical stimulation (TES) during a slight voluntary contraction peripheral stimulation. In both **B** and **C** repetitive stimulation had no facilitatory effect on the MEPs. Responses are the average of ten trials for TMS and five trials for TES. Average M-waves before and after repetitive stimulation for the same subject are shown in **D**

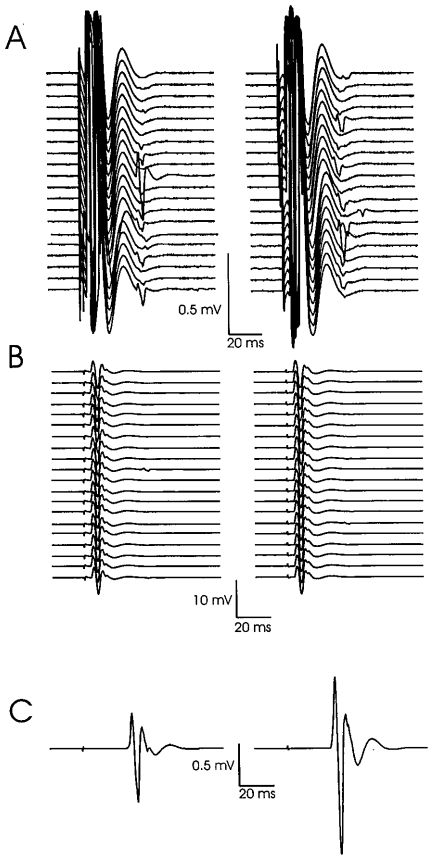

Fig. 6 **A** F-waves recorded in FDI before (left) and after (right) a 2-h period of repetitive ulnar nerve stimulation at the wrist. There is no significant change in either the number or average amplitude of F-waves ($P>0.05$). **B** same traces as in **A** but gain reduced to show M-waves clearly. Note the change in calibration. There was no significant difference in the M-waves after the repetitive peripheral stimulation. **C** Average (of ten) MEPs recorded in the relaxed FDI after TMS. The MEPs and F-waves were recorded in the same trial, with the order of presentation of magnetic stimuli and supramaximal peripheral nerve stimuli pseudo-randomised. The response seen after the period of ulnar nerve stimulation (right) is significantly larger than that recorded before nerve stimulation (left). The intensity of magnetic stimulation was 120% of motor threshold for the relaxed FDI

t-test $P>0.05$). There were no significant changes in F-wave characteristics. The mean F-wave amplitude before stimulation was 130±34 μV and after stimulation it was 117±35 μV ($P>0.05$). The mean F-wave area before stimulation was 90.9±5.3 μVms and after stimulation it was 95.6±5.4 μVms ($P>0.05$). F-wave incidence (out of a maximum of 15) was 12.0±2.7 (mean±SD) and 8.5±2.7 before and after stimulation, respectively (paired *t*-test, $P>0.05$). The M- and F-wave data recorded in one subject, together with the MEPs evoked before and after ulnar stimulation, are shown in Fig. 6.

Discussion

The novel finding of the present study is that a prolonged period of peripheral nerve stimulation can induce a specific and significant increase in the size of MEPs evoked in hand muscles by brain stimulation. Only muscles innervated by the stimulated nerve showed a facilitation of MEPs evoked by brain stimulation, while an adjacent muscle innervated by a different nerve showed no such change.

The increased response to stimulation of the motor cortex after a period of peripheral nerve stimulation is similar to observations in animal models. Clark et al. (1988) and Recanzone et al. (1990) have shown that prolonged stimulation of afferent pathways that converge at the cortex can induce consistent alterations in sensory cortical organisation in the monkey and cat, respectively. In the present study, repetitive stimulation of the ulnar nerve at the wrist simultaneously activated ulnar-innervated muscles in the hand and their afferents. Therefore, it is likely that this stimulation produced a convergent input from these stimulated muscles to the sensorimotor cortex.

It may be inferred from the animal data that the increases in cortical responsiveness seen in the present

study reflect an increase in the area of cortical territory projecting to the muscles that were stimulated (FDI and ADM). It is tempting to relate the increased MEP response area evoked from a number of cortical sites to the increases in receptive field size seen in animals. Ridding and Rothwell (1995) have pointed out that an increase in the excitability of an existing projection would lead to a similar result; however, the absence of a change in cortical threshold may be evidence against this possibility. The observation that responses in APB (innervated by the median nerve) were not altered by ulnar nerve stimulation indicates that the effect is specific rather than a global effect of prolonged peripheral nerve stimulation. Changes of a similar nature have been described very recently in swallowing musculature (Hamdy et al. 1998). These authors demonstrated that a brief period of pharyngeal stimulation resulted in an increase in the amplitude of responses evoked in that muscle by magnetic stimulation of the brain. However, the responses recorded were extremely small and whether the changes represent alterations in primary motor cortex organisation is open to debate.

Effect of digital stimulation

Digital nerves are overwhelmingly cutaneous and lack muscle afferents. When the digital nerves to digits 4 and 5 were stimulated in a manner analogous to the (mixed) ulnar nerve stimulation employed in the main series of experiments, there was no significant increase in the areas of MEPs evoked in the three muscles investigated. This finding suggests that cutaneous input alone is not sufficient, at least over this time-frame, to produce a change in the excitability of the corticospinal projection. Whether this means that muscle afferents have a more important role in driving these excitability changes needs further investigation.

Level of excitability change

It was not possible in the present study to establish with certainty the level within the corticospinal pathway at which the stimulation-induced increase in excitability occurred. We used two approaches to determine whether the changes in excitability were at the spinal or cortical level. Firstly, we employed F-waves to investigate if there was any evidence for a change in spinal motoneurone excitability after the period of peripheral nerve stimulation. There are a number of limitations in utilising F-waves as an indicator of excitability change in the spinal motoneurones. Firstly, it is likely that the population of motoneurones tested by F-waves is not the same as that activated by the descending corticospinal volley produced by TMS, even though there may well be some overlap in the population of cells activated. Secondly, although F-waves are used routinely in a clinical setting to assess spinal excitability changes there is some evidence that F-waves are an imperfect indicator of spinal motoneuronal excitability (Hultborn and Nielsen 1995). Therefore, the F-wave studies need to be interpreted with caution. However, the fact that there was no significant change in F-wave incidence, amplitude or area at least supports the proposal that the changes seen with TMS are unlikely to be due to a major increase in excitability of the ulnar motoneuronal pool (see Eisen & Odusote 1979).

Another possible site for excitability change needs to be considered. It is likely that at least some component of the MEP evoked by TMS is produced by transmission through spinal interneurones (Pauvert et al. 1998). Excitability change within these circuits is not investigated by F-wave measurements. While we cannot rule out a contribution from spinal interneurones in the excitability changes documented in the present study, we are unaware of any evidence supporting the idea that afferent input is capable of altering transmission in these pathways. Therefore, the available data suggest that the source of the MEP facilitation is most likely to lie within the motor cortex.

It is difficult to investigate this problem further with the electrophysiological techniques currently available. Due to their different sites of cortical activation, the techniques of TMS and TES have been used to provide evidence that excitability changes are localised to the cortex (Thompson et al. 1991; Day et al. 1991; Macefield et al. 1996). A change in corticospinal excitability that is evident with TMS but not TES suggests that the excitability change is confined to the motor cortex. However, responses to TES in relaxed muscle are very small or absent. In subjects in whom it is possible to evoke responses, very high stimulus intensities are required. At threshold the descending volley to TES is dominated by D-waves, while at higher intensities of stimulation I-waves are recruited (Katayama et al. 1988; Day et al. 1989). Therefore, at high stimulus intensities TES activates the cortex in a manner much more analogous to that of TMS activation and the ability to localise excitability change to the cortex is compromised. It has been shown previously that voluntary contraction effectively masks corticospinal excitability changes produced after manipulations in afferent input (Ridding and Rothwell 1995). In order to confirm this previous finding, we performed a series of experiments where the effect of repetitive peripheral nerve stimulation was examined with brain stimulation under three different conditions. Firstly, we used TMS with the subjects completely relaxed. As expected, and in agreement with the findings of the main series of experiments, we found a significant increase in MEP amplitudes after the 2-h period of peripheral stimulation. However, using TMS and TES during slight voluntary contraction of the target muscle (FDI), we were unable to demonstrate any facilitation of MEPs after the peripheral stimulation. These findings agree with previous reports that voluntary contraction can mask excitability changes produced by alterations in afferent input (Ridding and Rothwell 1995). Therefore, un-

der these experimental conditions, TES has little to offer in terms of providing evidence for the site of excitability change.

Distribution of excitability change

The largest percentage change in MEP area in FDI after the 2-h period of peripheral stimulation takes place at more lateral sites (see Fig. 3). This is in contrast to the changes seen in the non-stimulated APB muscle. In APB, at more lateral sites, there was a reduction in MEP area. It is, therefore, tempting to suggest that the increase in MEP area seen in FDI at these more lateral sites occurs at the expense of responses in APB. This may be analogous to the finding from intracortical mapping experiments in animals where denervated or functionally quiet cortex becomes "invaded" by adjacent functionally active regions (e.g. Nudo et al. 1996). However, analysis of the CoG of each muscle representation demonstrates that there was no significant change in the distribution of the cortical map and, therefore, we must be circumspect with our interpretation of these findings. It may be that with greater subject numbers a significant effect could be found.

While we did not exhaustively investigate the time-course of the increased amplitude of MEPs after the end of stimulation, our preliminary findings indicate that the change in excitability lasts for at least 15 min. Therefore, the increase in excitability is unlikely to be the result of a transient increase in neuronal excitability. These findings are consistent with previous reports that changes of a similar nature persist for 30–60 min after periods of altered peripheral input (Hamdy et al. 1998; Ziemann et al. 1998). The complete time-course of this effect is being investigated in an ongoing series of experiments.

The underlying mechanisms for these changes in excitability and organisation are unknown. However, given the rapidity of the changes after the intervention, it is likely that normally ineffective or weak synapses may have become disinhibited or "unmasked" such that they influence cortical activity (Sanes and Donoghue 1992).

Implications

The present findings may lead eventually to practical applications in rehabilitation. For example, it may be possible to increase the cortical representation of muscles weakened by stroke by stimulating the motor innervation of the weak muscle concurrently with a functionally-related normal muscle. In such situations, when the aim is to "remodel" the motor cortex, peripheral nerve stimulation offers important advantages over performance of motor tasks. It is not known whether nerve stimulation is more effective than training tasks in producing change within the sensory (Byl et al. 1996) and/or motor cortex (Nudo et al. 1996). However, nerve stimulation is more precisely controlled, requires no conscious effort, and may be more appropriate when paresis is severe and limiting.

Summary

These findings show for the first time in humans that peripheral nerve stimulation can result in specific alterations in the excitability of the corticospinal projection to hand muscles. These findings may be analogous to those reported in animals after peripheral nerve stimulation or behavioural training tasks and may have important implications for the neuro-rehabilitation of patients.

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