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RESEARCH ARTICLE

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Input-output properties and gain changes in the human corticospinal pathway

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Abstract Experiments were done to determine the form of the input-output relation (i.e. stimulus intensity vs response amplitude) of the corticospinal pathway of the first dorsal interosseous and the tibialis anterior, respectively. Our purpose was to determine from these quantitative relations which input-output parameters would be useful measures in studies dealing with motor cortical task dependence. The motor cortex was excited by focal transcranial magnetic stimuli and the evoked motor response were recorded with surface electromyographic electrodes. In some experiments the discharge probability of single motor units in response to magnetic stimuli of increasing intensity was determined from intramuscular recordings. For both muscles the form of the input-output relation was sigmoidal. The steepness of the relation increased, up to 4–7 times the value at rest, with increasing tonic background activity. The threshold decreased, but only slightly, with increasing tonic background activity. The minimum value of the threshold was reached at activation levels of about 10–20% of the maximum tonic effort, whereas the steepness of the relation reached its maximum at higher activation levels, typically about 30–40% of the maximum tonic effort. These observations imply that these two input-output parameters of the corticospinal pathway – one reflecting the bias level (threshold) and the other the gain (slope) – are determined by different neural mechanisms. The plateau level of the sigmoidal input-output relation was not influenced by the background activation level, except that in some subjects (4/9) it could not be reached when no background motor activity was present. This was probably due, for the most part, to limitation of the maximum stimulator output. Additionally, this finding may reflect a change in the intrinsic excitability of the motor cortex in going from rest to activity, or that convergent inputs from different descending and afferent systems are required for maximal activation of motoneuron pools. Thus, the threshold, steepness and plateau level characterize the input-output parameters of the human corticospinal pathway for a given level of motor activity. In contrast to the nonlinear input-output relation of the corticospinal pathway as whole, which includes the motoneuron pool and any spinal interneuronal relays, the discharge probability of all single motor units was a linearly increasing function of the stimulus strength ($r \geq 0.9$, $P<0.01$). Thus, the sigmoidal input-output relation of the corticospinal pathway, as a whole, is not due to the input-output properties of single motoneurons. The possible neural mechanisms which underlie the shape and parameters of the input-output relation as well as the methodological implications of the results are considered.

Key words Motor cortex · Magnetic stimulation · Corticospinal pathway · Single motor units

Introduction

In normal humans and neurological patients, the non-invasive method of transcranial magnetic stimulation (TCMS) of the motor cortex was initially used to determine the conduction times, the form of the evoked motor responses (EMRs), their dependence on background voluntary activity, and the response of single motor units (SMUs) (see the review by Mills 1991). More recently, adaptive changes in the spatial characteristics of the motor cortical map have begun to be investigated in patients who suffered strokes, limb amputation, or spinal cord injuries and in blind Braille readers (Levy et al. 1990; Pascual Leone et al. 1993; Kew et al. 1994).

Additionally, following work on the task dependence of spinal reflexes (see review by Stein and Capaday 1988), TCMS has also begun to be used to study the involvement of the motor cortex during various motor tasks ranging from postural maintenance to voluntary manipulation of objects by the hand (Datta et al. 1989; Flament et al. 1993; Nielsen et al. 1993; Abbruzzese et

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al. 1994; Lavoie et al. 1995). Surprisingly, however, the form of the relation between stimulus intensity and motor response (i.e. the input-output relation) is not known. This is a necessary requirement for quantitative studies of the involvement of the motor cortex during different motor tasks. Knowledge of the input-output parameters may also be useful for understanding certain details in studies dealing with plasticity of the motor cortex.

The amplitude of EMRs increases as a function of the background voluntary activity in an approximately linear manner, at least for the tibialis anterior (TA) and the soleus (Maertens de Noordhoot et al. 1992; Lavoie et al. 1995); but apparently not so for the first dorsal interosseous (FDI), in which the response saturates very rapidly as a function of the background level of motor activity (Hess et al. 1987). In either case, the form of the input-output relation cannot be deduced from these observations. In the present study we have determined the form of the input-output relation of the corticospinal pathway of an intrinsic hand muscle (the FDI) and a leg muscle (the TA). In each case, the input-output relation was determined over the full range of stimulus intensities, from threshold to saturation, and at several levels of voluntary activity. From these quantitative relations we determined which input-output parameters would be useful measures in studies dealing with motor cortical task dependence. In addition, we have also determined from recordings of SMU discharge to what extent the input-output relation of the corticospinal pathway, as a whole, is determined by the behaviour of single motoneurons. A short account of some of the present findings has been published as an abstract (Devanne et al. 1995).

Materials and methods

The experiment were done on nine healthy subjects (5 male and 4 female) ranging in age between 25 and 49 years (mean 31 years, SD 8.1 years). All subjects participated with their informed consent in accordance with the Declaration of Helsinki. The experimental procedures were approved by the local ethics committee. The subjects were screened for any history of epilepsy, or the presence of metal fragments in the eye or brain.

Electromyographic recordings and magnetic stimulation

Bipolar electromyographic (EMG) recordings from the TA were obtained from two pairs of surface Ag-AgCl disc electrodes (diameter 9 mm, separation 3 cm) placed over the belly of the muscle below the motor point. The electrodes were attached to the skin by O-rings of double-sided adhesive film and firmly secured by overlying elasticized straps for the TA, or adhesive tape for the FDI. The electrodes used to record the EMG activity of the FDI were similar to those used for the TA, except that the recording surface was 1 mm in diameter. The electrodes were shielded right up to the recording surfaces and connected to an optically isolated preamplifier by a shielded twisted-pair cable. The twisted pair cable reduces magnetic interference from the stimulating coil. The reference electrode, a large metal plate (3 cm×9 cm) covered in gauze and moistened with saline, was placed high on the subject's arm on the side of the recordings and connected to the common input of the preamplifiers.

The EMG signals were amplified, high-pass filtered at 20 Hz, and low-pass filtered at 1 kHz, prior to sampling (4 kHz) by an analogue-to-digital converter (A/D). The same EMG signals were also rectified and filtered (20–100 Hz) for sampling by a separate A/D channel. Electrical stimuli of 0.5 ms duration were applied to the common peroneal nerve near the head of the fibula, or the ulnar nerve just above the wrist. The stimulus strength was adjusted to elicit a maximum M-wave in the TA and FDI, respectively. This served to provide an index of motor activation capacity against which to compare cortically evoked motor responses.

Magnetic stimuli were applied over the scalp using a Cadwell MES-10 electromagnetic stimulator, of maximum magnetic field strength 2 T, with a coned, double-D shaped, focal coil (16 cm×8 cm). The coil was placed in contact with the scalp with the long axis of the intersection of its two loops pointing forwards and the coil handle backwards. For activation of the TA the coil was placed parallel to and approximately 0.5–1.0 cm lateral to the midline and its mid-point was aligned antero-posteriorly against the vertex (Cz). Stimulation employing this coil orientation was found to evoke the lowest threshold and most selective activation of the contralateral ankle musculature (Lavoie et al. 1995). For activation of the FDI the coil was similarly placed over C3. Fine adjustments of coil position were made at the beginning of the experiments to identify the optimal locations for each subject. Surface markings were then drawn onto the scalp to serve as a reference grid against which the coil was positioned. The coil was maintained on the head by the experimenter and its position and orientation were constantly checked to ensure that no slippage occurred during the experiment. Mechanical fixation of the coil on the head is not well tolerated by subjects and is not – given the obvious limitations – reliable.

The magnetic stimulus pulses were of 70 µs duration and their intensity was measured as a percentage of the maximum current which could be discharged through the coil. The inter-stimulus interval (ISI) in the experiments involving EMRs varied between 2 and 4 s. These intervals were used to minimize fatigue in these protracted experiments. As a result of this, and the above precautions on coil positioning, the responses obtained were very stable and reproducible (Fig. 3). No attempt was made a eliminating the first response of a series at the same stimulus intensity (Flament et al. 1993) because it was not de facto the largest response of a series. For the SMU experiments, which involved much weaker stimuli, the ISI varied between 1.5 and 2.5 s. The time intervals between stimuli were pseudorandom and equi-probable. Randomization of ISIs tends to average out the effects of ISI on EMR amplitude. None of the presently reported effects can be due the influence of ISIs, since the same random ISI parameters were used at all contraction levels.

Single motor unit recordings

SMUs in either the TA or the FDI were recorded differentially by two microwires, each 50 µm in diameter. The cut end of each microwire served as the recording surface. The other end of each microwire was stripped of its insulation over about 2 cm and served as a connection to the amplifier's input cable. Both wires were inserted into a 27-gauge needle and hooked back 2–3 mm from the needle tip. All assembled electrodes were sterilized and used only once. The needle was inserted into the muscle with appropriate aseptic precautions and then withdrawn leaving the microwires in place. These were connected to a shielded twisted-pair cable by small springs. The cable was connected to an optically isolated amplifier. A conventional time-amplitude window discriminator was used to generate the acceptance pulses for each discharge of the motor unit. The acceptance pulses were counted by the computer to generate a peri-stimulus time histogram (PSTH) of the discharge of the SMU in response to the magnetic brain stimuli in real time. The bin width of the PSTHs was 0.5 ms. The stimuli, typically 128 at each intensity, were delivered at random with respects to the inter-spike interval of the SMU. The total number of counts in each bin was divided by the number of stimuli, thus expressing the PSTH in terms of discharge probability.

Experimental procedures

The procedures for the experiments involving EMRs of the TA and the FDI were generally the same. Subjects sat in a chair and faced an analogue meter placed 1 m in front of them. The meter was calibrated so that a full-scale deflection of the needle corresponded to the maximum sustained isometric contraction of the muscle, as measured by the rectified and filtered (bandpass 10–20 Hz) surface electromyogram. In the experiments on the TA, subjects were comfortably seated with one leg partially outstretched. The angle of the knee joint was approximately 140° and that of the ankle joint was approximately 120°. The foot was positioned on a tilted platform and tied to it by a large adjustable strap against which subjects voluntarily dorsiflexed the ankle. Subjects were required to contract steadily the TA of one ankle to generate and accurately sustain varying target levels of the muscle's maximal EMG activity, while maintaining the muscles of the other leg in a relaxed state. For the experiments on the FDI the subject's right forearm rested on a table in the prone position with the distal joint of the index finger placed in a mould attached to a rigid stop.

The experimental procedure required the subject to exert a prescribed level of tonic activity during which the motor cortex was activated with stimuli of increasing intensity. At each stimulus intensity and tonic activation level, 8 to 16 magnetic stimuli to the motor cortex were delivered and the EMRs averaged and displayed in real time. The order of presentation of the stimuli (i.e. random vs ordered) has no effect on the form of the relation, nor its parameters (Fig. 3). Thus, the usual procedure was to increase the stimulus intensity starting at a value about 5% below threshold and increasing it in steps of 2–5% until saturation of the EMRs. This method allowed us to determine – by monitoring the responses on a storage oscilloscope – on which portion of the input-output relation we were operating during the course of the experiment. In this way a sufficient number of points were obtained near the foot of the relation and on the plateau; these are critical for good convergence of the curve-fitting procedure. The procedure was repeated at several contraction levels (typically 10%, 20%, 30%, and 40% of maximum voluntary contraction) as well as when the subject was relaxed. The order of required contractions was random.

Data reduction and analysis

At each stimulus intensity and contraction level the rectified and unrectified EMRs were averaged over a time segment of 250 ms, including 50 ms prior to the stimulus. The peak-to-peak (p-p) value and integral of the averaged responses were calculated and plotted against the stimulus intensity. The contraction level was calculated as the mean value of the rectified and filtered EMG over the 50-ms time segment prior to the stimulus. Inspection of the scatter plots of EMR size versus stimulus intensity clearly revealed that the relation between the two variables had a sigmoidal shape. The Boltzmann sigmoidal function was used to fit the data points by the Levenberg-Marquard nonlinear least-mean-squares algorithm (Press et al. 1986). This function is used, for example, to describe activation and inactivation of ionic conductances as a function of membrane potential. The Boltzmann equation relating the amplitude of the response (EMR) and the stimulus intensity (S) is given by the following equation:

$$\mathrm{EMR(S)} = \frac{\mathrm{EMR_{max}}}{1+\exp\left[(\mathrm{S_{50}}-\mathrm{S})/K\right]} \tag{1}$$

This equation has three parameters: the maximum value ($\mathrm{EMR_{max}}$) or plateau of the relation, the stimulus intensity ($\mathrm{S_{50}}$) required to obtain a response 50% of the maximum, and the slope parameter (K). The inverse of the slope parameter (1/K) is directly proportional to the maximal steepness of the function, which occurs at $\mathrm{S_{50}}$. For example, halving the slope parameter doubles the steepness of the relation at $\mathrm{S_{50}}$.

The thresholds of the input-output relations were estimated by fitting the data points on the steepest part of the relation by a straight line (Willer et al. 1987). The threshold, or *x*-intercept, was then calculated from the regression parameters. This was done because the threshold is neither an explicit parameter of the Boltzmann equation, nor can it be derived from the equation. Alternatively, the $\mathrm{S_{50}}$ parameter could be used to estimate the change of threshold, but not the threshold per se. However, if the steepness of the relation changes, the change in the $\mathrm{S_{50}}$ parameter is no longer proportional to the change of threshold. In any case with either method, or visual inspection of the data, it was clear that the change of threshold was relatively small (see Results).

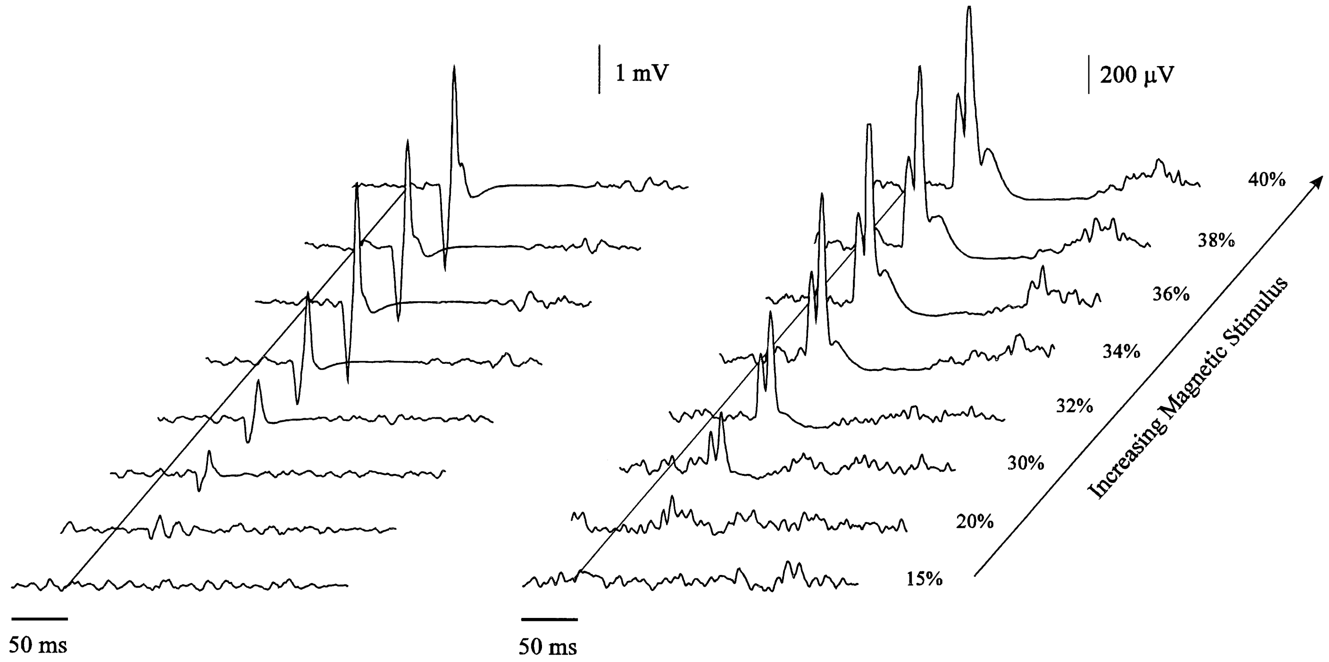
Results

This section is divided into two parts. In the first part we describe the quantitative relation between EMR amplitude and stimulus intensity at several different levels of tonic voluntary contractions. These measurements represent the input-output relation of the corticospinal pathway as a whole and how the parameters of this relation change as a function of the level of contraction. In the second part, the relation between the discharge probability of SMUs and the intensity of the magnetic stimuli to the motor cortex is presented. This section addresses the issue of the relation between the response properties of the system and the single elements within it.

Relation between EMR size and stimulus intensity

Figure 1 illustrates a typical example of the form of the TA EMRs and their increase with stimulus intensity. The amplitude of the unrectified EMRs increased with increasing stimulus intensity from threshold to saturation, generally with little change in the form of the response. At strong stimulus intensities, however, a small additional potential usually appeared at the end of what where essentially biphasic responses. This is most readily apparent in the rectified traces shown in Fig. 1. The p-p amplitude of the EMRs and their integral are very strongly correlated (Lavoie et al. 1995), so that either may be used as a measure of EMR size. With either measure we found that the relation between the size of the EMR and the stimulus intensity had a sigmoidal shape (Figs. 2, 3). In general, however, when the Boltzmann sigmoidal function was fitted to the data points the coefficient of determination (R^2) was higher when the integral was used as a measure of the size of the response. This was probably because the small late-potential which often appears at strong stimulus intensities contributes to the value of the EMR integral but not to its p-p amplitude. The form of the relation between EMR area and stimulus intensity is shown in Fig. 2 for the TA and the FDI. In each case, the shape of the relation is sigmoidal. The Boltzmann equation fits always accounted for at least 80% of the total variance of the data points (i.e. $R^2 \geq 0.8$) and were a statistically better fit than a straight line ($P<0.01$).

The data presented in Fig. 3 address the issue of variability and reproducibility of the EMRs obtained in the present experiments. The coefficient of variation (CV) of the EMRs was inversely proportional to EMR amplitude



Non-Rectified Rectified

Fig. 1 Typical surface electromoygraphic (EMG) recordings of evoked motor responses (EMRs) of the tibialis anterior (TA) obtained in a subject exerting a constant voluntary contraction of about 10% of maximum voluntary contraction (MVC). Responses to stimuli of increasing strength are aligned from *front* to *back* as indicated on the *right-hand side* of the records. The *angled line* traversing the records indicates the time of stimulation

(Fig. 3). Thus, larger responses are inherently less variable than smaller ones. The CV was typically around 0.5 for threshold responses, and 0.1 for EMRs of maximal amplitude. Additionally, the data shown in Fig. 3 illustrate that our method of coil fixation and the other experimental procedures we used (rigorous control of the tonic activation level, randomization of ISIs, etc.) provide highly reproducible responses. The input-output curves shown in Fig. 3 were measured approximately 1:30 h apart in the same subject maintaining a tonic activation of the TA at 10% of maximum voluntary contraction (MVC). There is no statistical difference between the two sigmoidal input-output curves, nor between the fitted lines relating the CV to EMR amplitude.

The most salient feature of the input-output curves shown in Fig. 2 was that the steepness of the relation increased as a function of the tonic activation level. The maximal slope, an index of the overall steepness of the relation (see Materials and methods), was calculated from the fitted parameters for each tonic activation level. The relation between maximal slope and the level of tonic voluntary contraction is shown in the middle graphs of Fig. 2. For both muscles, the maximum slope of the sigmoidal input-output relation increased from its value at rest and usually peaked at about 30–40% of MVC. The steepening of the relation with increasing contraction level was a very strong and robust effect. For the data set as a whole, the maximum slope increased on average 4-fold (sd 1.9), in going from rest to 30–40 % of MVC (min. to max. 2–7 times). For the TA the maximal slope increased on average 4.7-fold (sd 2.0) over the above range of contractions. For the FDI the average increase was 2.7-fold (sd 0.7).

The plateau level of the TA was on average about 20% of the Mmax value and for the FDI it was approximately 45% of Mmax. The plateau level was essentially the same for all levels of TA contraction in five of six subjects. The higher plateau value for a TA contraction level of 30% in the one subject was probably due to cross-talk pickup from adjacent muscles. Signals generated by distant sources typically contain lower-frequency components (Lindström and Petersén 1983; Capaday 1996). Thus, spectral analysis of the unrectified EMRs showed that, in this subject, low-frequency components (peak at 30 Hz) appear at high stimulus intensities when the contraction was maintained at 30% MVC. The plateau level was reached in four of six subjects in the relaxed state for the TA. In the remaining two, it appeared that failure to reach the plateau level attained during voluntary activity was probably due to limitation of the maximum stimulator output. In each case inspection of the scatterplots, such as the one in Fig. 2, revealed that the responses at the highest possible stimulus intensities were on a slowly increasing portion of the input-output curve. The situation for the FDI was somewhat different. In two of three subjects the plateau attained during voluntary contractions was clearly higher than that attained at rest. Such instances cannot be explained by limitations of the maximum stimulator output and may reflect limitations of the neural circuitry in the absence of excitatory inputs associated with voluntary activity.

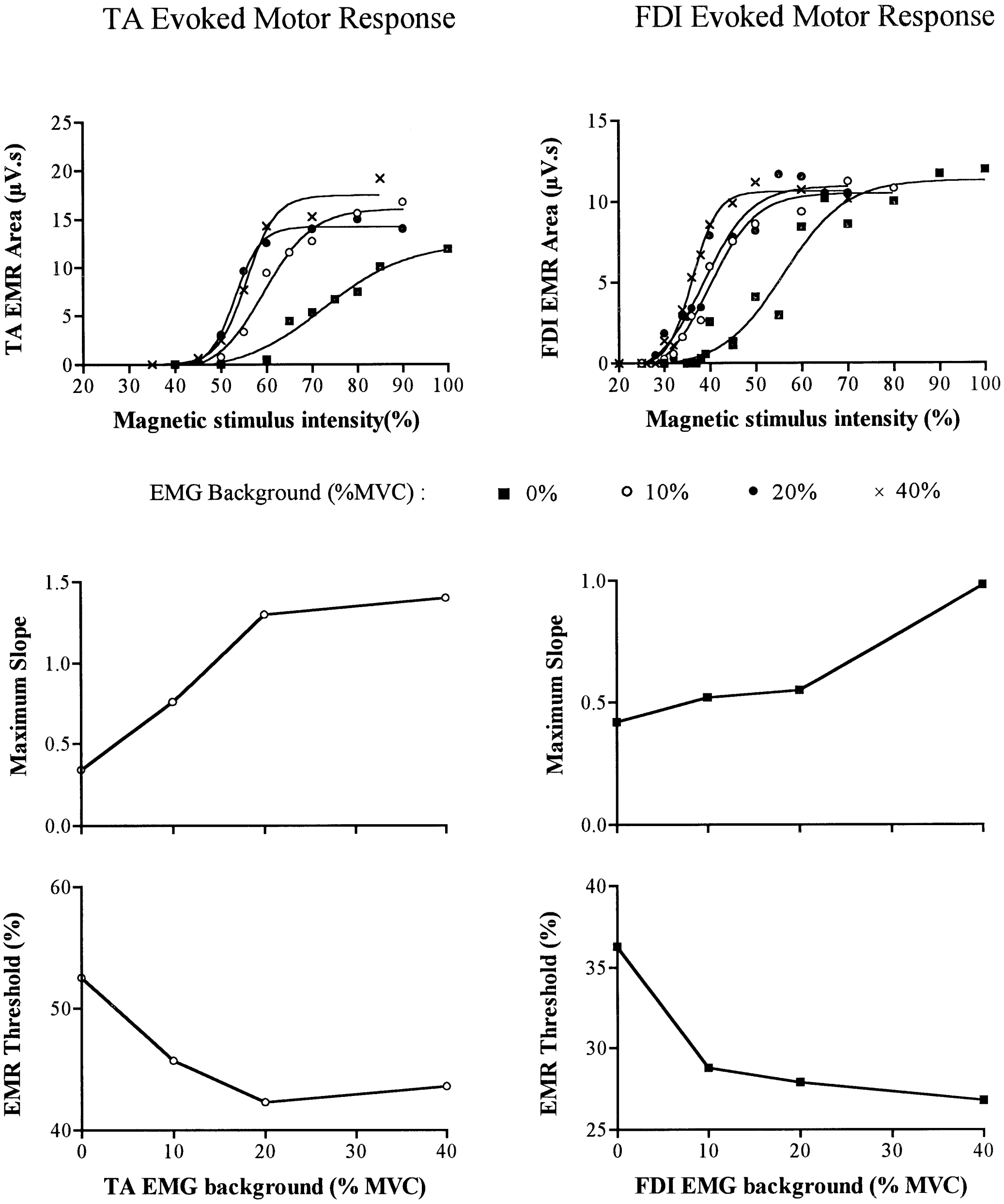


Fig. 2 Representative examples, from two different subjects, of the quantitative relation between stimulus intensity and EMR amplitude are shown in the *topmost graphs* for the TA and the first dorsal interosseous (FDI). Note the sigmoidal nature of the relation in each case. In the *middle graphs* the slope at the steepest part of each of the fitted sigmoidal functions above (i.e. maximal slope) is plotted against the percentage of MVC exerted by the subject. Finally, the *bottom graphs* plot the estimated threshold, of each of the sigmoidal functions above, against the percentage of MVC exerted by the subject. The data from the TA are from a different subject from that in Fig. 1

The threshold of the input-output relation decreased with increasing levels of tonic contraction as can be seen in the lowermost graphs of Fig. 2. The decrease of the threshold was, however, relatively modest compared with the changes observed for the slope. Typically, the threshold decreased by some 15–40% of its value at rest. The threshold reached its minimum value at about 10–20% of the MVC, in both muscles.

Response of SMUs to magnetic stimuli of increasing intensity

The results presented in this section were obtained in three subjects in whom two SMUs were recorded in the FDI and four in the TA over a wide range of stimulus intensities. The recorded motor units were not in general the lowest threshold units. They were selected on the basis of a stable motor unit potential at contractions strengths typically 10–15% of MVC. The discharge probability of all SMUs in both muscles increased as a linear function of the stimulus intensity, an example of which is shown in Fig. 4. The Pearson-product-moment linear correlation coefficient (*r*) was, in all cases, at least

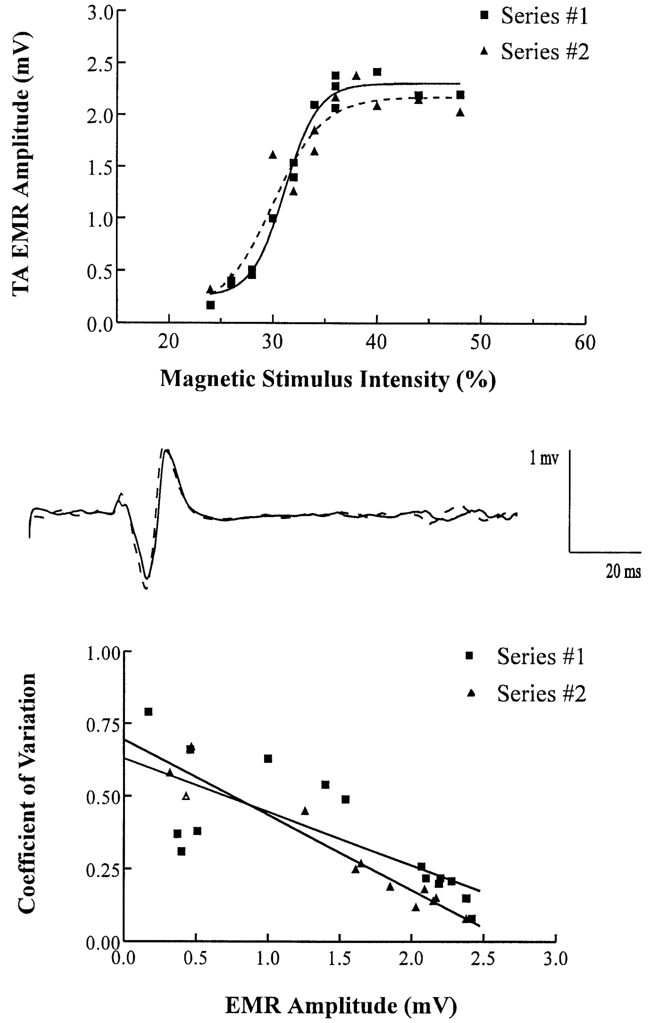


Fig. 3 An example addressing the issue of variability and reproducibility of EMRs obtained in the present experiments. The input-output curves shown in the *top graph* were measured about 1:30 h apart in the same subject. The coil was repositioned for the second series of measurements on the same landmarks over which it was positioned for the first series of measurements. There is no statistical difference between the two curves (i.e. fitting a curve to each data set separately does not increase the total variance accounted for compared with fitting a single curve to the data set as a whole). In the *middle figure* two averaged (n=8) EMRs obtained around 1:30 h apart in response to stimuli of 32% of the maximum stimulator output are superimposed. Note the nearly identical amplitude and waveform. The *bottom graph* relating the coefficient of variation to the EMR amplitude makes the point that responses obtained at a later time in the experiment were no more variable than at the beginning. The order of presentation of the stimuli was random in each experiment. The subject maintained a tonic voluntary contraction of 10% of MVC

0.9 ($P<0.01$). In marked contrast, the population response (i.e. the EMR), measured from surface EMG recordings simultaneous with the SMU discharges, increased sigmoidally (Fig. 4). In no case was there any clear curvature near the x-intercept of the relation between discharge probability and stimulus strength which was so clearly evident for the population response (Fig. 4). The PSTHs at five different stimulus intensities are also shown in Fig. 4; these are part of the data set on the adjacent scatterplot. It can be seen that the short latency peak (ca 30 ms), representing the stimulus-induced increase in discharge probability, increases in amplitude with increasing stimulus. The duration of the short-latency peak, approximately 4 ms, changed relatively little and thus remained very synchronous over the range of stimulus strengths used. Finally, the SMU potential was nearly identical at the beginning and at the end of the experiment (inset diagrams in Fig. 4).

Ancillary observations

The duration of EMRs increased in an approximately linear manner with increasing EMR amplitude. The correlation between these two variables was moderately strong (r values were typically between 0.7 and 0.9, $P<0.05$). Considering the TA, the y-intercept of the relation was significantly smaller ($P<0.05$) for the data points obtained at 10–20% of MVC compared with those obtained at rest. The average of the y-intercept obtained at rest was 21.9 ms (SD 5.6 ms) and that obtained at 10–20% of MVC was 14.2 ms (SD 2.07 ms). Thus, EMRs of the same amplitude are briefer in duration when evoked upon an background level of motor activity than when evoked at rest. This may imply that the discharge of motor units contributing to the EMRs is more synchronized when the motoneuron pool is active.

Discussion

The corticospinal pathway taken as a whole includes the cortical circuitry, the motoneuron pool and its intrinsic properties, as well as any spinal interneuronal relays. Three main findings on this pathway are reported in the present paper. The first is the characterization of the form of the input-output relation of the corticospinal pathway to an intrinsic hand muscle (FDI) and to a leg muscle (TA). The form of the relation is in both cases sigmoidal, and thus strongly nonlinear. Secondly, the form of the input-output relation for the corticospinal pathway as a whole is not dependent on the input-output behavior of single motoneurons. The detailed reasons for this are considered in the next section. The third and most striking result was that the steepness, or equivalently the gain, of the relation changes as a function of the level of motor activity of the same qualitative task. This input-output parameter, and the others measured in the present study, most likely reflect the excitability properties of the population of corticospinal neurons contributing to the EMRs as well as those of the motoneuron pool – including any interneuronal relays in the pathways such as propriospinal neurons (e.g. Burke et al. 1994). In the discussion which follows, four issues are dealt with: the mechanisms underlying the shape of the input-output relation, those involved in the increase in slope and de-

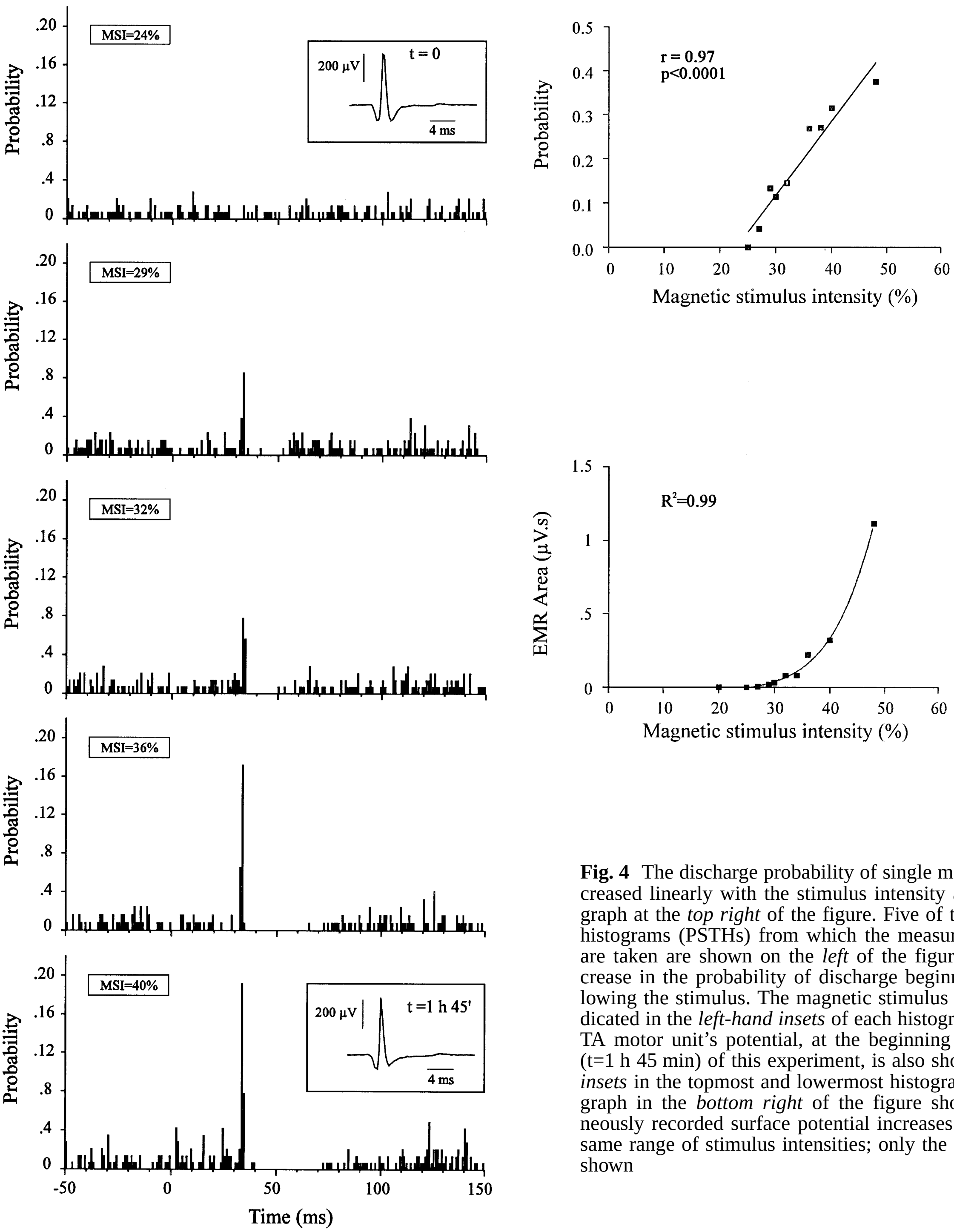


Fig. 4 The discharge probability of single motor units (SMUs) increased linearly with the stimulus intensity as can be seen in the graph at the *top right* of the figure. Five of the peri-stimulus time histograms (PSTHs) from which the measurements in that graph are taken are shown on the *left* of the figure. Note the sharp increase in the probability of discharge beginning some 30 ms following the stimulus. The magnetic stimulus intensity (MSI) is indicated in the *left-hand insets* of each histogram. The shape of this TA motor unit's potential, at the beginning (t=0) and at the end (t=1 h 45 min) of this experiment, is also shown in the *right-hand insets* in the topmost and lowermost histograms, respectively. The graph in the *bottom right* of the figure shows that the simultaneously recorded surface potential increases sigmoidally over the same range of stimulus intensities; only the foot of the relation is shown

crease in threshold with increasing motor activity, and finally the methodological implications of the results.

Before proceeding, it will be useful to consider what cortical elements are excited by the magnetic stimuli. Our present understanding is that the currents induced by the magnetic stimuli activate corticospinal neurons trans-synaptically, producing so-called I-waves, and directly at the initial segment or beyond, producing so-called D-waves (see details in Amassian et al. 1987; Edgley et al. 1990; Burke et al. 1993; Baker et al. 1994; Mazzocchio et al. 1994). However, the details on the exact mode of activation, such as which of the two responses comes first, remain controversial. Nonetheless, nearly all these studies strongly support the idea that magnetic stimuli with a figure-of-eight coil, as well as a round coil, produce EMRs that depend on the excitability of the motor cortex, whether they are produced by I-waves, or by D-waves generated close to the initial segment (see Mazzochio et al. 1994 for a somewhat different point of view). It should also be kept in mind that beyond threshold the cortical stimuli elicit corticospinal volley with multiple components. Therefore, the input-output relations measured in the present study are the result of multiple descending volleys.

Mechanisms underlying the shape of the input-output relation

The sigmoidal shape of the input-output relation is most likely due to a combination of the following factors: the way cortical elements are recruited by the magnetic stimuli, the multiple components of the corticospinal volley, the recruitment of motoneurons with progressively larger motor unit potentials (Henneman, 1957), and perhaps a greater tendency for synchronization of SMU discharges with increasing stimulus strength (Poliakov and Miles 1992).

On the other hand, it is clear that the shape of the input-output relation of the corticospinal pathway is not dependent on the input-output relation of single motoneurons. This follows from the fact that the discharge probability of single motoneurons, as measured by the discharge of their motor unit, increases linearly as a function of the magnetic stimulus intensity. Evoked motor responses are the result of summation of nearly synchronous motor unit potentials. The expected value, or average, of each motor unit's contribution to the population response is a potential, E(S), whose size is given by the product of the maximum motor unit potential, A_{smu}, and the probability of discharge, P(S), at a given stimulus intensity. The expected value is thus a linearly increasing function of the stimulus intensity: $E(S)=P(S)\times A_{smu}$. The experimentally observed linear relation between motoneuron discharge probability and the stimulus intensity is consistent with the model proposed by Ashby and Zilm (1982), in which the motoneuron membrane potential rises linearly towards the firing threshold. It is also consistent with the motoneuron pool model of Capaday and Stein (1987) in which the motoneurons are modelled by nonlinear Hodgkin-Huxley like equations.

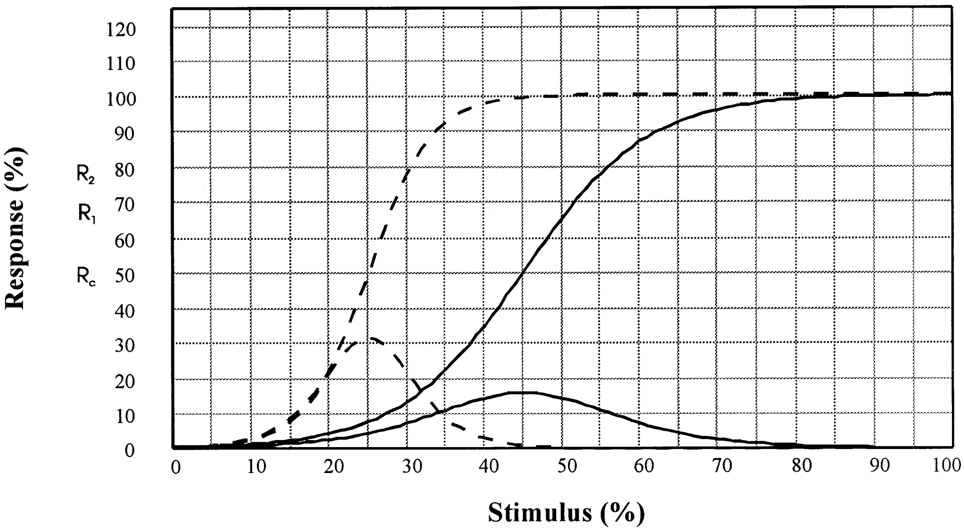
The factors which are likely to contribute to the observed shape of the input-output relation are considered next. Recruitment of motoneurons with constant-amplitude motor unit potentials would produce a linearly increasing input-output curve. Since the experimentally measured input-output curve is nonlinear it must, at least in part, reflect the well-known fact that stimuli of increasing strength recruit motoneurons with increasing motor unit potentials (Henneman 1957). Indeed, sigmoidal input-output relations occur in systems composed of excitable elements with a wide distribution of spike amplitudes. For example, the compound action potential of nerves (Erlanger and Gasser 1937) and monosynaptic reflexes of the cat spinal cord (Rall 1955; Hunt 1955) increase as a sigmoidal function of stimulus intensity. However, unlike compound action potentials whose input-output relation is fixed, that of monosynaptic reflexes and EMRs will depend on additional modulating influences arising from the properties of the neural circuitry. These additional factors will serve to determine the exact parameters of the relation, such as its steepness. Thus, the characteristics of recruitment of motoneurons and corticospinal neurons will influence the threshold and steepness of the relation (Heckman 1994). Additionally, increased synchronization of motor unit discharge and the multiple corticospinal volleys may well contribute to the steep portion of the sigmoidal relation. Unfortunately, for a fixed level of background activation no simple measure of synchronization can be derived from the present data, but the possible contribution of this factor can be tested empirically. Double, or multiple, discharges of single units with increasing stimulus intensity occur rarely (Day et al. 1989). This phenomenon is therefore not expected to contribute significantly to the present observations. Finally, the plateau value of the input-output relation is probably not the maximal response to a purely excitatory corticospinal volley. More likely, it represents a balance between excitatory and inhibitory components of the corticospinal volley, including recurrent inhibition of late recruited motoneurons by those recruited earlier.

Mechanisms involved in the increase of slope and decrease of threshold

The threshold of the response reflects the stimulus intensity needed to activate the most excitable corticospinal elements and motoneurons. Clearly, increasing the excitatory bias at the cortical and segmental level will be decrease the threshold stimulus intensity. Since the most excitable motoneurons become active at low levels of motor activity (and probably also corticospinal neurons), it follows that the threshold will reach its minimum value rapidly as a function of motor activity, as observed in the present experiments.

On any of the input-output curves of the same family (e.g. Fig. 2) responses of equal amplitude represent the summed discharge of essentially the same motoneurons, according to the principle of orderly recruitment (Henneman and Mendell 1981). It follows that an increase in the steepness of the relation represents an increase in gain, but not a change in the order of recruitment. A nonlinear relation between the size of the subliminal fringe of the corticospinal pathway as a whole – i.e. the respective subliminal fringe of cortical neurons, spinal interneurons and motoneurons – and the level of motor activity (Capaday and Stein 1987) may be a factor underlying the increase in slope with increasing motor activity. Thus, a cortical stimulus would activate a number of motoneurons in proportion to the level of motor activity and the size of the associated subliminal fringe. A large subliminal fringe during motor activity, compared with a smaller one at rest, would lead to more rapidly increasing responses. It may also be suggested that a consequence of increased gain is an increased synchronization

Fig. 5 The *dashed sigmoidal curve* at its steepest portion (50% of maximum) has twice the slope of the other sigmoidal curve. The *bell-shaped curves,* corresponding to each sigmoidal function, are the differential functions calculated for a 5% increment in stimulus intensity. This figure graphically illustrates the consequences of nonlinear input-output relations for interpreting experimental results, as discussed in the text



of motor unit discharges. This can explain why EMRs of the same amplitude are briefer in duration when evoked upon a background level of activity compared with those evoked at rest. In summary, gain changes as a function of the level of motor activity may be a built-in feature of the organization of the corticospinal pathway.

Functional implications

Although in the present experiments an artificial expedient – magnetic brain stimulation – was used to characterize the input-output relation of the corticospinal pathway, the same characteristic changes in input-output parameters, such as gain, should manifest themselves during natural motor activity. It will be interesting to design new experiments addressing these issues.

Methodological implications of the results

Our motivation for doing these experiments was to determine which input-output parameters would be useful measures in studies dealing with the involvement of the motor cortex in various types of motor tasks. From the foregoing it is clear that at a constant level of motor activity the threshold, maximal slope and plateau value completely characterize the input-output relation of the corticospinal pathway in a given task. Task-dependent differences should be reflected in changes in one or more of these parameters. A clear demonstration of a task-dependent change in the involvement of the motor cortex would require, at least in part, that these parameters be shown to be statistically different at comparable levels of activity. Additional criteria are discussed in Capaday (1996)

The present results are also pertinent to more traditional approaches in which activation of the motor cortex is used as either a test or conditioning stimulus. The nonlinear nature of the input-output relation of the corticospinal pathway, and especially the change in steepness which occurs as the background level of motor activity is increased, are important considerations. For example, the sigmoidal input-output relation of the corticospinal pathway implies that the amount of facilitation or inhibition of a test EMR is a function of its amplitude. Furthermore, there is no range on such a curve over which the amount of facilitation or inhibition is either constant, or relatively so, because the first derivative of a sigmoid curve is bell shaped and, thus, has no plateau (Fig. 5). More importantly, the increase in steepness of the relation with background level of motor activity means that the system can operate on different input-output curves and implies that the amount of facilitation or inhibition produced by an added conditioning stimulus will depend on the level of motor activity (Fig. 5). In the graphical example shown in Fig. 5 the dashed input-output curve at its steepest portion has a slope twice as great as the other curve. For each curve we calculated the differential function, which approximates the change in output expected for a small change in input (i.e. conditioning stimulus). Thus, for example, starting at a stimulus level which produces, in each case, a response of 50% (indicated as R_c on Fig. 5), and added 5% increment of the stimulus will in one case increase the response to 65% (R_1) and in the other to 80% (R_2). It follows that adjustment of the stimulus intensity to compensate for the effect of changes in the background activity on EMR amplitude is not a valid procedure for ensuring that the amount of facilitation or inhibition be independent of the test response amplitude, as is done with monosynaptic spinal reflexes (Hultborn et al. 1987; Crone et al. 1990). The same argument applies when activation of the motor cortex is used as a conditioning stimulus. Clearly, measuring the entire input-output relation of the corticospinal pathway in different tasks at matched levels of motor activity overcomes these problems.

Finally, it seems evident that these issues are ripe for further experimental studies and computer simulations of mathematical models aimed at identifying the mechanisms involved in the presently observed phenomena. Any new insights will improve our approach and understanding of the neural mechanisms of human motor control.

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