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Journal of Neuroscience Methods 74 (1997) 201–218

JOURNAL OF NEUROSCIENCE METHODS

Neurophysiological methods for studies of the motor system in freely moving human subjects

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Abstract

In this paper, the following experimental methods for studies of the motor system in freely moving human subjects will be considered: (i) eliciting the H-reflex and understanding its use as a test response, (ii) methods to measure reciprocal inhibition between antagonist muscles, (iii) methods to measure presynaptic inhibition of Ia-afferent terminals in the spinal cord, (iv) certain aspects of the interpretation of peri-stimulus time histograms (PSTH) of single motor unit discharge, and finally, (v) stimulation of the motor cortex and the measurement of response parameters that may reflect task dependent changes. Two closely related ideas bearing directly on these methods will be emphasized—the influence of the background level of motor activity on input–output properties of the neural pathway investigated and the operating point on the input–output curves at which the experimental variable is measured. Finally, in the discussion a simple model that is easily understandable in geometric terms is presented to help predict and interpret the outcome of these sorts of experiments. © 1997 Elsevier Science B.V.

Keywords: Reflex; Spinal cord; PSTH; EMR; Motor unit; Motor cortex; Motor control

1. Introduction

The study of the motor system in freely moving humans during natural motor activities, such as walking, running and postural adjustments allows for an understanding at the systems level of how neural circuits actually work. For example, the input–output properties of several spinal cord neural circuits have been shown to change as a function of the motor task (see Stein and Capaday, 1988 for stretch reflexes; Evans et al., 1989 for cutaneous reflexes). These changes are quantitative in nature, i.e. they involve changes of the parameters of input–output relations. It has been suggested that they serve to adapt the motor system to the biomechanical requirements of the task (Stein and Capaday, 1988; Capaday, 1995). Additionally, it may be possible that neural circuits subserving motor control are modified in a more fundamental manner, that is at the level of the architecture of the circuit (Pearson, 1985; McCrea, 1994; Pearson and Collins, 1993; Capaday et al., 1995). It can be argued that the basic principles of human motor control are best determined by studying freely moving subjects during natural motor tasks, because the motor system is inherently designed to control such tasks. Finally, this research has clear applications to understanding the basis of pathophysiological conditions following damage to the CNS (e.g., spasticity following stroke or spinal cord injuries).

This article contains a review of several neurophysiological methods that are commonly used to study the mechanisms of motor control in humans. I will specifically address how these methods can be used to study the neural basis of motor control in freely moving human subjects. These methods offer clear advantages that will be duly described in each section; but as with any scientific method, the limitations must also be clearly understood. Two ideas will be emphasized throughout: (i) the importance of controlling the background level of motor activity upon which a particular measurement is made and (ii) the need to understand

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PII S0165-0270 97)02250-4

the nature of the input–output properties of the pathway under study. Much of the theoretical and experimental foundations of these methods go back to the pioneering studies of Renshaw (1940), Lloyd (1941), and Lundberg (1966; 1970; 1975). The reader should refer to these classic papers as an introduction to the physiological basis of the methods described herein. Sherrington's seminal discoveries and conceptual influence must also be acknowledged (Sherrington, 1906).

It must be recognized, however, that the initial development of these methods was done on reduced animal preparations in what may be called the 'resting state' (i.e., lacking background motor activity). Therefore, proper application of these methods in behaving human subjects and interpretation of the results require particular attention to the above two propositions (Capaday et al., 1990).

2. Methods and results

In this section the following experimental methods will be considered: (i) eliciting the H-reflex and understanding its use as a test response, (ii) methods to measure reciprocal inhibition between antagonist motoneuron pools, (iii) methods to measure presynaptic inhibition of Ia-afferent terminals in the spinal cord, (iv) certain aspects of the interpretation of peri-stimulus time histograms (PSTH) of single motor unit (SMU) discharges and finally (v) stimulation of the motor cortex and the measurement of response parameters that may reflect differences in task dependence. Methods for the study of cutaneous reflexes will not be considered in the present review. The reader is referred to the following papers which contain detailed methodological sections on the issue (Garnett and Stephens, 1980; Yang and Stein, 1990; Burke et al., 1991). Other important experimental methods which are not described in the present article include: galvanic stimulation of the vestibular apparatus (Lund and Broberg, 1983), ischemic block of peripheral afferents (e.g., Dietz et al., 1979), differential decrease of afferent fibre conduction velocity by local cooling (Paintal, 1965; Matthews, 1989) and local anesthesia of peripheral nerves (Matthews and Rushworth, 1957; Gassel and Diamantopoulos, 1964).

2.1. The H-reflex

What does the H-reflex (Hoffmann, 1918) test for? A comprehensive answer to this apparently simple question remains to be formulated. Clearly, this issue is important for interpreting results obtained by this method. One common, but gravely flawed, answer is that the H-reflex reflects the excitability of the α-motoneurons. The excitability of the motoneurons is an intrinsic property which depends on the total membrane conductance, the membrane potential relative to threshold, and the presence of neuromodulators such as 5-HT (Schwindt and Crill, 1984; Kiehn, 1991). However, the intrinsic excitability of the α-motoneurons is not the only factor involved in the net output of the motoneuron pool as a whole. Synaptic transmission at the Ia-afferent terminals is controlled by presynaptic inhibitory mechanisms (Rudomin, 1990) and the terminals possess complex time, amplitude, and use dependent release properties (Eccles, 1964; Crone and Nielsen, 1994). We suggested on the basis of neural modeling studies and animal experiments that for a fixed level of α-motoneuron pool activity and stimulus intensity, the H-reflex output depends on the level of presynaptic inhibition of Ia-afferent terminals in the spinal cord (Capaday and Stein, 1987a, 1989). In other words, the H-reflex is a measure of the efficacy of synaptic transmission when measurements are made at matched levels of motor activity. While this is an improvement on the above view, knowledge of two additional factors is required to make such an assertion. One, which has already been mentioned, is the novel and intriguing finding that neuromodulator substances such as 5-HT (serotonin) can change the intrinsic excitability of the α-motoneurons. Thus, it is conceivable that even if the stimulus intensity and level of motor activity are the same in two different motor tasks the excitability of the motoneurons may be greater in one task because of, for example, greater release of 5-HT (Heckman, 1994). The second factor that must also be known is the rate of recruitment, or equivalently the recruitment gain as defined by Kernell and Hultborn (1990). Thus, if the H-reflex is operating on a steeper input–output curve in one task than in another, a stimulus of fixed strength will elicit a larger reflex response despite the fact that the background level of motor activity may be the same. The recruitment gain can, at least in principle, be measured experimentally with present methods. This has already been done for the human corticospinal pathway during voluntary activity (Devanne et al., 1995, 1997) and will be dealt with in detail further on. Finally, the intrinsic excitability of motoneurons and the recruitment gain of the motor pool may be related factors (Devanne et al., 1995, 1997).

The H-reflex is most commonly studied in the soleus muscle. In what follows the emphasis is on methods to study the H-reflex in this muscle, but similar considerations apply to other muscle groups such as the quadriceps and the wrist flexors (Dietz et al., 1990; Day et al., 1984). A simple and effective electrode (cathode) for stimulating the tibial nerve in the popliteal fossa is a recessed –AgCl electrode placed over the nerve, usually at a site somewhat above or below the popliteal

fossa itself, and surrounded by a rubber strap to maintain pressure on the electrode (Capaday and Stein, 1986; Capaday et al., 1995). This often makes it easier to control the stimulus intensity during walking because the movement of the electrode relative to the nerve is somewhat less than if the cathode is placed in the crease of the popliteal fossa. The anode, which usually consists of a large metal plate (e.g., stainless steel or brass) covered with gauze and wetted in saline is placed on the opposite side of the knee just above the patella; modern adhesive type electrodes of similar surface area are equally good. The idea behind this stimulation arrangement is that because the impedance of the tissues across the leg is relatively constant (Hugon, 1973) the stimulating current would also be relatively constant. The Simon-type electrode (Simon, 1962) offers little or no advantage over a simple surface electrode, and subjects may find it uncomfortable during movements of the leg. However, as explained further below, since the objective is to maintain a constant amplitude M-wave it matters little whether the stimulator is a constant voltage or constant current source. In practical terms a constant current source does no better than a constant voltage source. The stimulus duration is an important parameter since it allows for a separation of the threshold of Ia-fibres from that of α-motor fibres. In our experience a stimulus duration of 0.5 ms is a good compromize between the need to separate thresholds and the need to minimize unpleasant sensations (Fig. 1). In general, this stimulus duration gives a better separation of the threshold of Ia-afferent fibres from

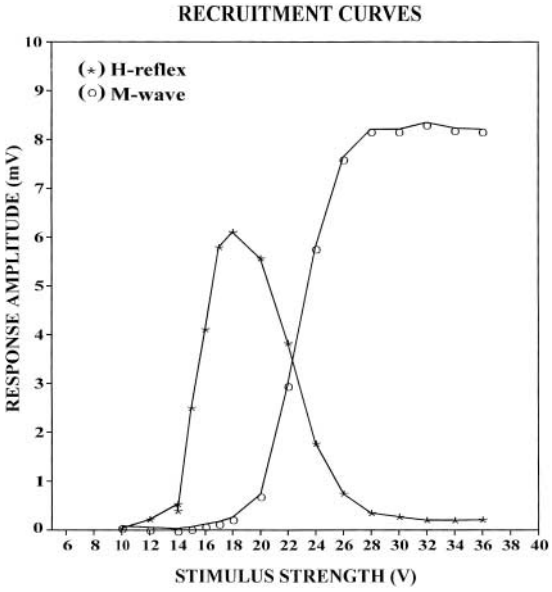

Fig. 1. H-reflex and M-wave recruitment curves obtained with a stimulus duration of 0.5 ms. Note the clear separation of the threshold of group I afferent fibres and that of the α-motor fibres. Note also the obvious sigmoidal shape of the early portion of the H-reflex recruitment curve.

that of α-motor fibres compared to a stimulus of 1 ms duration. Briefer stimuli would further separate the thresholds, but the necessarily greater stimulus intensities required makes such stimuli unpleasant, because nociceptive nerve terminals in the skin will be stimulated. A brief summary of the theory of nerve stimulation based on the strength-duration equation is given in the appendix. Ideally experiments should begin once the impedance between the recording electrodes has stabilized, since this affects the size of the recorded potentials. Additionally, the experimenter may wish to periodically measure the recording electrode impedance during the course of an experiment.

Movement of the cathode relative to the nerve is the main technical factor limiting trans-cutaneous stimulation at constant intensity over the course of an experiment. During tasks such as walking and running the large angular displacement of the knee produces large displacements of the cathode relative to the underlying nerve. However, even during tasks involving no apparent movement of the knee, such as during quiet standing or isometric activation while seated, contraction of the underlying muscles may displace the stimulating electrode away from the nerve. Monitoring the stimulating current alone does not guarantee that the same number of nerve fibres are stimulated at different times in the same task, at different contraction levels of the same task, or in different tasks. A constant current stimulator will maintain the stimulus current essentially constant over relatively large changes of load impedance; but because of possible changes in distance and orientation of the cathode relative to the nerve the current across the nerve and thus the number of fibres stimulated will be different. At present, the best measure of stimulus intensity is the M-wave amplitude (response of the α-motor fibres to direct stimulation of the nerve). The assumption is that stimulation of a constant number of α-motor fibres also ensures stimulation of a constant number of afferent fibres (Capaday and Stein, 1986). There is one possible caveat to this argument; the nerve fibres, whether afferent or efferent, should not be discharging at or near their maximum rate because this may make them more refractory to a stimulus of fixed strength. In general this has not been a problem, for example, the relative refractory period of human nerves is between 4 and 5 ms, whereas the highest discharge rates of soleus motor units is between 10 and 15 spikes/s (i.e., one spike every 60–100 ms). Therefore, only a small fraction of motor axons will be refractory at any time. Nonetheless, for each task investigated the possible discharge rates of afferent and efferent fibres relative to their refractory period should be considered (Capaday and Stein, 1986; Capaday et al., 1995).

When exactly should the M-wave amplitude be measured? The amplitude of an M-wave can change dra-

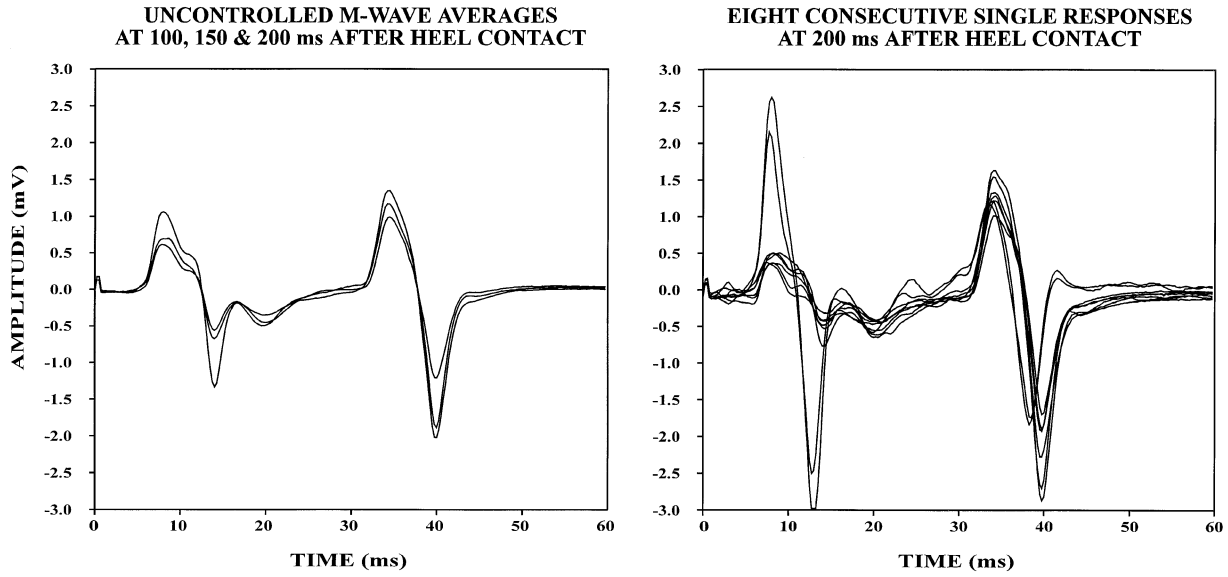

Fig. 2. The amplitude of the M-wave, and thus the effective stimulus strength, can change within 50 ms or less during the step cycle, or at the same point in different step cycles. These records were obtained by setting the stimulator output at a fixed value (e.g. 40 V) and accepting all responses. There was, thus, no control of the M-wave amplitude. The traces on the left graph are averages of eight responses. These experiments were done on the soleus muscle.

matically within 50 ms or less in the same step, or at the same point in different step cycles (Fig. 2). It follows that in order for the M-wave amplitude to best reflect the stimulus intensity it should be measured immediately after delivery of the stimulus. Furthermore, especially in tasks involving movement of the joint or different levels of contraction, a constant intensity stimulus cannot be guaranteed for a sub-motor threshold stimulus; even if it is followed some 50 ms later by supra-motor threshold stimulus that elicits an M-wave of the desired amplitude. This restricts, to some extent, stimulation at so called pure group Ia intensity. But this is a limitation that at present cannot be overcome in tasks involving freely moving subjects. The M-wave can be measured by a conventional time–amplitude window comparator, an adaptive waveform recognition system (Miles et al., 1989), or a time–amplitude window comparator implemented as part of the data acquisition software (Capaday et al., 1995). The latter method allowed for the simultaneous control of the intensity of stimulation of two antagonist nerves during walking, which otherwise would have been extremely difficult. In any case, only responses having M-waves that fall within the prescribed time-amplitude window should be acquired and averaged with similar responses.

The above procedures allow the experimenter to obtain H-reflex responses to stimuli of essentially the same intensity at different levels of activity in the same task and in different tasks. This allowed us, for example, to suggest task dependent changes in the efficacy of synaptic transmission between the Ia-afferents and the α-motoneurons (Stein and Capaday, 1988). However, a limitation of this approach is that the system is only tested at a single stimulus intensity. As explained further below, in the section on 'Stimulation of the Human Motor Cortex', characterizing the system over the entire input–output range can be much more revealing. The input–output curve of the human H-reflex cannot be characterized in its entirety, because of collision of the orthodromic and antidromic spikes along the motor axons. Nonetheless, it may be possible in some circumstances to obtain a number of data points between threshold and the plateau level of the H-reflex recruitment curve. Augmenting the stimulus duration from 0.5 ms to 1 ms may increase the number of H-reflexes associated with an M-wave and thus increase the range over which controlled H-reflex measurements can be make.

The background level of motor activity at the time the H-reflex is measured is also a very important variable. For a stimulus of fixed strength the amplitude of the H-reflex depends on the level of activity of the motor pool. H-reflexes of small or large amplitude relative to Mmax, a measure of maximum recruitment of the motor pool, increase approximately linearly and relatively slowly with the background level of motor activity, as measured by the mean value of the rectified and filtered EMG or the joint torque (Gottlieb et al., 1970; Capaday and Stein, 1986, 1987b). H-reflexes of intermediate size also increase approximately linearly with the background level of motor activity, but much more steeply. The reasons for this are explained in Section 3 where a simple model of the input–output

properties of the motoneuron pool is presented. In any case, a clear task dependent change of the input–output properties of the H-reflex, or indeed any other motor pathway, must at the very least occur independently of the level of motor activity. For example, in a recent study we re-examined the effects of instructions given to subjects on the size of the M2 stretch reflex response of the flexor pollicis longus muscle (FPL). The response was measured at several tightly controlled levels of FPL activity. It was found that while the size of the M2 response was strongly dependent on the background level of motor activity, in contrast the subject's intention on how to react to the perturbation had no additional effect (Capaday et al., 1994). This clearly contradicted a widely held assumption. Additionally, the background level of motor activity may have some hitherto unsuspected effects on the input–output properties of the motoneuron pool. We have recently found that the recruitment gain of the human corticospinal pathway depends on the background level of motor activity (Devanne et al., 1995, 1997). This is probably also true for other motor pathways. The implication is that in a given task the monosynaptic reflex may operate on different input–output curves depending on the level of motor activity. This issue and its implication for neurophysiological studies of the human motor system is treated in detail in sections Section 2.3 and Section 3.

The joint torque and the mean value of the rectified and filtered EMG are strongly correlated during isometric contractions, but not for other types of contractions (Milner-Brown and Stein, 1975). Furthermore, the joint torque lags the EMG by some 50 ms, it is produced by the activity of all muscles acting at the joint, and the same torque can be produced by either reciprocal activation or co-contraction of antagonist muscles. For these reasons the EMG is the better estimate of the level of activity of a motor pool. The mean value of the rectified and filtered EMG is related to the number of active motoneurons and their discharge rate (Milner-Brown and Stein, 1975; De Luca, 1979). As long as motor units increase their discharge rate in parallel with the EMG and are recruited in the same order in the different tasks investigated (Milner-Brown and Stein, 1973; Desmedt and Godaux, 1978; Grimby, 1984; Hoffer et al., 1987), the mean value of the rectified EMG will be a fair measure of the level of activity of the motor pool. However, in comparing tasks in which the degree of synchronization of motor unit discharge may be widely different, such as ballistic contractions compared to more slowly graded contractions, the same mean value of the rectified EMG may not represent the same combination of active motor units and discharge rate. How the number of active motoneurons, their discharge rate and the degree of their synchronization is related to the mean value of the rectified EMG is not known, but computer models bearing on this issue are currently being developed (Fuglevand et al., 1993)

2.2. Reciprocal inhibition between antagonist muscles

Reciprocal inhibition between antagonist muscles is subserved at the segmental level by a pathway which is at least disynaptic (Eccles, 1964). It is important to keep in mind that this pathway is under strong supraspinal control, as are all other segmental reflex pathways (Lundberg, 1975; Jankowska, 1992). It is also important to distinguish the phenomenon of reciprocal inhibition—relaxation of the antagonist muscle during activity of the agonist (Sherrington, 1913)—from the neural mechanisms which produce it. A comprehensive review of the control of the disynaptic reciprocal inhibitory pathway during different types of motor tasks has been recently published (Crone and Nielsen, 1994).

There are, at present, four methods by which reciprocal inhibition can be studied in humans: (i) by measuring the depression of ongoing EMG activity (Agarwal and Gottlieb, 1972; Capaday et al., 1990), (ii) by conditioning-testing (C–T) paradigms where the conditioning stimulus may be applied to a peripheral nerve or to the motor cortex (Crone and Nielsen, 1994; Nielsen et al., 1993b), (iii) by observing the 'free' behavior of the H-reflex of the antagonist during activity of the agonist (Gottlieb et al., 1970; Lavoie et al., 1995a) and (iv) by observations of the discharge of SMUs in PSTHs (Ashby and Labelle, 1977; Kudina, 1980; Nielsen and Kagimara, 1992). The same principles of stimulation of peripheral nerves at constant intensity apply as for the H-reflex.

The method used by Capaday et al. (1990) is useful for determining the state of the inhibitory pathway to an active motor pool. This method was developed because of concern about the validity of C–T paradigms, whereby the nerve to the antagonist is stimulated shortly before the stimulus is delivered to the agonist nerve so as to elicit a test H-reflex. The H-reflex results from the synchronous discharge of α-motoneurons in response to a large excitatory postsynaptic potential (EPSP). Summation of small or moderately sized inhibitory synaptic potentials (IPSPs) produced by Ia-inhibitory interneurons (IaIns) may be incapable of significantly shunting the very large EPSPs, or hyperpolarizing the α-motoneurons, and so prevent the depolarization of the membrane to threshold. Therefore, inhibitory action on the α-motoneurons may go undetected when it is measured by its effect in reducing a large synchronous volley. Indeed, in most subjects it is difficult to show inhibition of a test H-reflex by this method. On the other hand, an IPSP will produce a delay of firing (i.e., reset the rhythm of a tonically discharging neuron). is in fact a sensitive test for the presence of IPSPs in cases where no obvious hyper-

polarizing potential is observed in intracellular recordings (Strowbridge et al., 1992). Such a delay of firing is clearly observed as a gap in the PSTH of repetitively discharging MUs following stimulation of the antagonist nerve at group I strength (Ashby and Labelle, 1977; Kudina, 1980). Similarly, the inhibition will produce a depression in the mean rectified EMG activity, which represents a weighted average of the PSTHs of all discharging motor units (see the appendix in Capaday et al., 1990). The method, therefore, has the merit of assessing inhibition by its effect in transiently decreasing the asynchronous motor activity which occurs under natural conditions. The obvious limitation of this method, and that of the closely linked PSTH method, is that it can only be used to measure the inhibition acting on an active motoneuron pool, or single motoneuron. The main result obtained by this experimental method is that the inhibition from antagonists remains operative during activity of the agonist(s). The amount of inhibition, measured from the average rectified and filtered EMG record as the difference between the mean background level and the mean level of the depression, increases linearly with the amount of motor activity as shown in Fig. 3 (Capaday et al., 1990; see also Matthews, 1986). It should not be concluded from this observation that the excitability of the IaIns from the antagonist increases with the level of motor activity of the agonist. Rather, the proportionality between the amount of inhibition and the background activity arises in a complex manner which is not yet fully understood

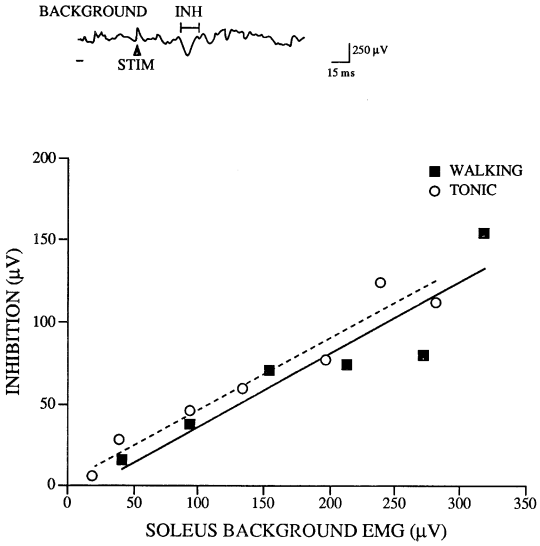

Fig. 3. Relation between the amount of inhibition and the background level of motor activity as measured by the mean value of the rectified EMG. The amount of inhibition was calculated as described in the text from records such as the one shown above the graph. In this example the amount of inhibition of the soleus produced by stimulation of common peroneal nerve was the same during tonic voluntary activity or during the swing phase of walking.

and which may simply result from a fixed level of IaIns excitability. The relative contribution of motor unit recruitment and firing rate modulation in the process of force gradation are essential factors to consider (Capaday et al., 1990). Thus, the linear relation between inhibition and the level of motor activity can be explained if newly recruited MUs are strongly inhibited by the stimulus, whereas previously MUs are inhibited relatively less as their firing rate increases; an idea consistent with the results of Miles et al. (1986) in the masseter muscle.

In applying the above method it may be noticed that in certain records a small peak precedes the depression of activity (e.g., see Fig. 5 in Capaday et al., 1995). This peak should not be interpreted as an excitatory response preceding the inhibition unless independent evidence such as PSTHs of SMUs is provided. Widmer and Lund (1989) showed that the small peak preceding the so called 'periodontal masseteric reflex' in rectified averaged records of masseter EMG activity is in fact the earliest sign of inhibition. They provided convincing evidence that this peak represents the synchronous repolarization of the last group of motor units active at the beginning of the inhibition (Matthews et al., 1988).

Postsynaptic inhibition and presynaptic inhibition are closely interwoven (Rudomin, 1990). It may well be that the neural basis of reciprocal inhibition depends on both mechanisms (Baldissera et al., 1981). C–T paradigms are particularly susceptible to the criticism that the measured effect on the H-reflex following a conditioning stimulation to the antagonist nerve depends not only on the state of the IaIns, but also on the existing level of presynaptic inhibition (or other presynaptic phenomena) of the afferent terminals conducting the conditioning volley (Capaday et al., 1995). Neurophysiological studies using C–T paradigms depend on maintaining a constant conditioning stimulus. This criterion can usually be met when dealing, for example, with anesthetized animal preparations. However, when this paradigm is used during motor activity, it is tacitly assumed that the task itself will not affect the conditioning stimulus. This is clearly not a tenable assumption without direct corroborating experimental evidence. Nielsen and Kagimara (1992, 1993a) have recently tried to disentangle the relative contribution of presynaptic inhibition and postsynaptic inhibition to the phenomenon of reciprocal inhibition. Corticospinal fibre terminals are not subject to presynaptic inhibition (Kato et al., 1978; Rudomin, 1990). Thus, an alternative to using the antagonist nerve as a conditioning input may be to use the corticospinal volley following stimulation of the motor cortex (Iles and Pisini, 1992; Nielsen et al., 1993b). However, especially when magnetic stimuli are involved, the composition of the descending corticospinal volley differs according to which muscle group is active, as described in Section 2.4.

Measuring reciprocal inhibition by its effects on the ongoing motor activity depends, for the most part, on postsynaptic effects since clear gaps of activity, due to hyperpolarizing potentials, are observed experimentally (Capaday et al., 1990). Presynaptic inhibition should simply reduce the firing rate of active motoneurons rather than produce gaps of activity. However, the level of presynaptic inhibition of the afferent fibre terminals transmitting the conditioning volley will affect the size of the induced IPSPs. Thus, for example, a task dependent change measured by this method cannot unequivocally be ascribed to a change at the level of the IaIns; but such an observation would, nonetheless, demonstrate a change of reciprocal inhibition in the functional sense.

It has been suggested that one of the requirements for proper application of the C–T method to measure reciprocal disynaptic inhibition is that the size of the test H-reflex must be the same at different levels of motor activity of the same task, or in different tasks (Crone et al., 1990). This is problematic in three respects. Firstly, it may not always be possible to obtain the same size H-reflex response at different levels of motor activity in the same task, or in different tasks (e.g., standing vs. the early stance phase of walking). Secondly, for example, if a comparison is made between rest and during motor activity, the test H-reflex stimulus in the active task may have to be lowered below the M-wave threshold. In such circumstances the experimenter cannot be sure that the same stimulus is applied to the nerve. Thirdly, as described in Section 2.3 and Section 3 the gain of the input–output curve on which the test H-reflex is operating may change as a function of the recruitment level of a motor task and at the same recruitment level in a different task (Devanne et al., 1995, 1997). Without knowledge of the gain at the operating point where the measurements are made, conclusions on possible differential effects of a conditioning stimulus are at best tenuous.

On the practical side, for studies dealing with reciprocal inhibition at the ankle, in most subjects a stimulus of about $1.3–1.5 \times$ MT to the common peroneal nerve near the head of the fibula produces an M-wave of nearly constant amplitude during all phases of the walking cycle (Capaday et al., 1990, 1995). For weaker stimuli, adjustments of the stimulus intensity must be made as discussed above.

2.3. Presynaptic inhibition of group Ia-afferent terminals projecting to motoneurons

A number of methods have been proposed to measure, in humans, presynaptic inhibition of group Ia-afferent terminals projecting directly to the motoneurons. These will be considered in the paper by Pierrot-Deseilligny in this issue and are the subject of a recent critical review by Stein (1995). Only a few comments bearing on this matter will be made here. In general, most of the points made above concerning the H-reflex and reciprocal inhibition are also applicable to measurements of presynaptic inhibition. Thus, one of the shortcomings of most methods proposed to measure presynaptic inhibition in man is that the background level of motor activity is not an explicitly controlled variable. Some methods make use of test H-reflexes of equal size in all motor conditions tested (Hultborn et al., 1987). This is in fact an attempt at controlling the activity level of the motor pool. However, H-reflexes of equal size may lay on input–output curves of different steepness depending on the background level of motor activity. Therefore, the amount of change produced by an added conditioning excitatory or inhibitory stimulus will depend on the steepness of the curve at the point where the test H-reflex is measured (Fig. 8). Additionally, most of these techniques depend upon using a peripheral nerve as a conditioning input with the tacit assumption that the conditioning input is itself not modulated in some way (e.g., presynaptically) by the motor task(s). Any change observed by using such methods cannot unequivocally be attributed to a change of presynaptic inhibition on the Ia-afferents used to elicit the test H-reflex (Capaday et al., 1995 for details). An improvement on using a peripheral nerve input, or any other input which may itself be modulated in some way by the motor task(s), is to use the corticospinal volley as a test-response in addition to the H-reflex. The effects of a conditioning stimulus, or task, can then be compared on each type of test response (Berardelli et al., 1987). However, as will be explained below, this method is limited to measuring changes of presynaptic inhibition when the test muscle group is active, but not when the antagonists are active.

2.4. Stimulation of the human motor cortex

A detailed account of the basic aspects of stimulation of the human motor cortex is presented in the paper by Rothwell in this issue. This section will deal with the application of this method to studies investigating task dependent changes of the link between the motor cortex and the motor circuits of the spinal cord (Datta et al., 1989; Flament et al., 1993; Nielsen et al., 1993b; Abbruzzese et al., 1994; Lavoie et al., 1995b). The following issues will be dealt with: (i) how to maintain the position of the coil on the head of freely moving subjects, (ii) what response parameters should be measured, (iii) if a task-dependent change is observed, how can the site of change be determined (e.g., intracortical vs. at the level of spinal cord interneurons), (iv) the implications of the observation that the response observed following stimulation at a given location on the motor cortex can be reversed by switching the back-

ground motor activity from agonists to antagonists and lastly (v) the detection of cross-talk artifacts in EMG recordings, an issue closely associated with the previous one.

Mechanical fixation of the coil on the head is not well tolerated by subjects and is not, given the obvious limitations, reliable. Manual fixation against a reference grid marked on the scalp is the simplest and most convenient way to maintain the position of the stimulating coil on the head (see details in Lavoie et al., 1995b; Devanne et al., 1995, 1997). This method has been used successfully during voluntary activity while sitting (Devanne et al., 1995, 1997), postural maintenance (Lavoie et al., 1995b), and walking (Capaday et al., 1996). It is reliable and provides very reproducible results as shown in Fig. 4. The two input–output curves of the tibialis anterior (TA) evoked motor response (EMR) measured 1.5 h apart are not statistically different. It can also be seen in that figure that the coefficient of variation of EMRs is inversely related to their amplitude (Devanne et al., 1997). Thus, larger responses are inherently less variable than smaller ones. On repetition of the measurements 1.5 h later, the relation between these two variables was not statistically different (Fig. 4). Equally reproducible results have been obtained by this method during walking (Capaday et al., 1996).

In the recent study by Devanne et al., 1995, 1997 we determined the form of the relation between stimulus intensity and motor response (i.e., the static input–output relation). Our motivation for doing these experiments was to determine which parameters of this relation would be useful measures in quantitative studies dealing with the involvement of the motor cortex in various motor tasks. As is evident from Figs. 4 and 5, the form of the input–output relation is sigmoidal and thus strongly nonlinear. The data were fitted by the Boltzmann sigmoidal function which is described in detail in Section 3. The same form of input–output relation was also found for an intrinsic hand muscle, the first dorsal interosseus (FDI) (Fig. 5). The mechanisms underlying the form of this non-linear input–output relation are discussed in Devanne et al. (1997). The most striking observation made in that study was that the slope of the relation increased markedly as the background level of motor activity increased (Fig. 5). 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 four fold (S.D. = 1.9), in going from rest to 30–40% of MVC (minimum–maximum, 2–7 times). The threshold decreased with increasing background motor activity, but much less so than the change of slope. The threshold reached its minimum at an activation level of about 10–20% of the maximum tonic effort, whereas the slope of the relation reached its

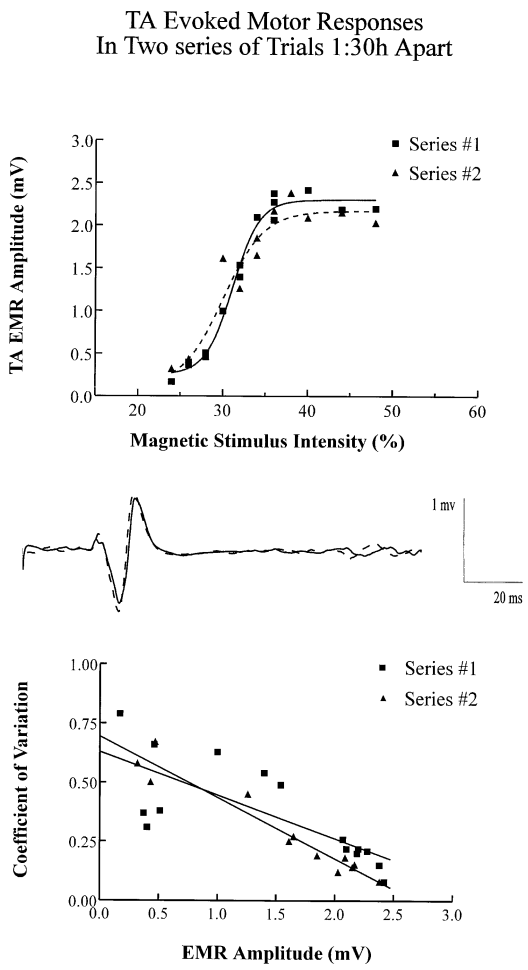

Fig. 4. An example addressing the issue of variability and reproducibility of EMRs obtained by the method of manual coil fixation. The input-output curves shown in the top graph were measured about 1.50 h apart in the same subject. There is no statistical difference between the two curves (i.e. fitting a curve to each data set separately does not increase the total variance accounted for compared to fitting a single curve to the data set as a whole). In the middle of the figure two averaged ($n = 8$) EMRs obtained around 1.5 h apart in response to stimuli of 32% of the maximum stimulator output are superimposed. Note the nearly identical amplitude and waveform. The graph at the bottom of the figure 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.

maximum value at activation levels of about 30–40% of the maximum tonic effort. This implies that these two input–output parameters—one reflecting the bias level (threshold) of the motoneuron pool 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 ity was present. This was probably due, for the most

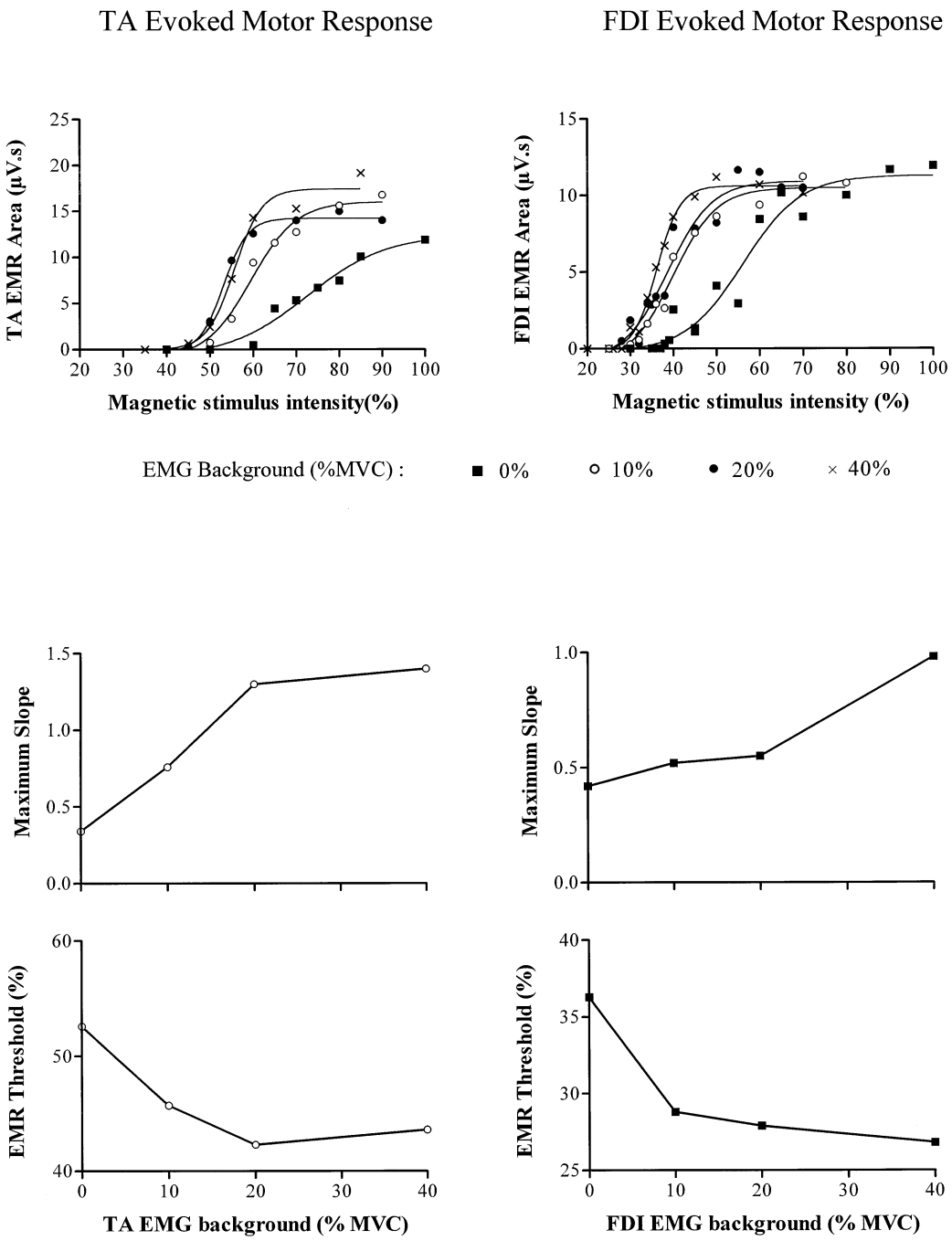

Fig. 5. Representative examples, from two different subjects, of the quantitative relation between stimulus intensity and EMR amplitude are shown in the topmost graphs for the TA and the FDI. Note the sigmoidal nature of the relation in each case. In the graphs in the middle of the figure the slope at 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 graphs at the bottom of the figure plot the estimated threshold, of each of the sigmoidal functions above, against the percentage of MVC exerted by the subject.

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. From the foregoing it is clear that, for a given level of motor activity, the threshold, maximal slope, and plateau value completely characterize the input–output relation of a task. A clear demonstration of a task-dependent change of the involvement of the motor requires that one or more of these parameters changes independently of the level of motor activity.

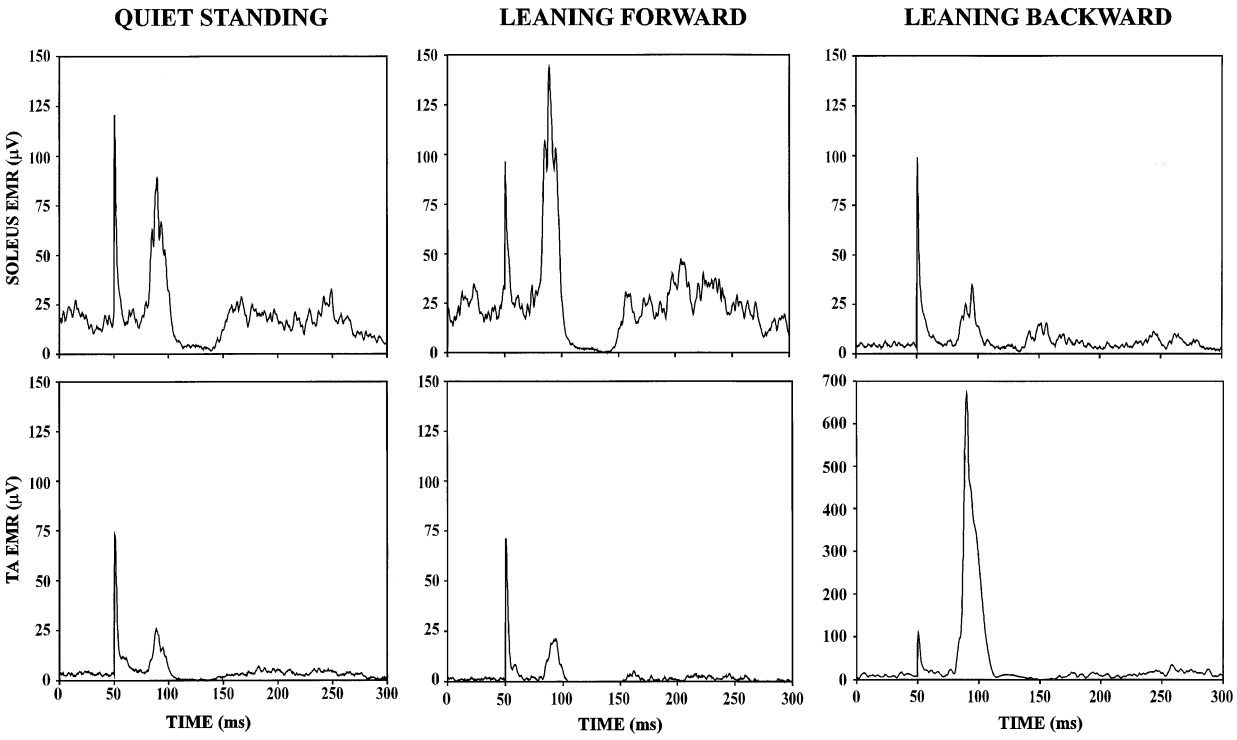

Fig. 6. The type of response observed following magnetic stimulation at a given position on the motor cortex depends on the background level of motor activity. In this example, stimulation with the center of the coil just lateral to the vertex produced a small response in the soleus during quiet standing, the response increased when the subject leaned forward, the response switched to activation of the TA when the subject leaned backwards. Note the different amplitude scale for the TA EMR on the graph in the lower right side of the figure.

If a task-dependent change is observed using this method, it does not follow that the site of change is intracortical. It may occur, for example, at the level of the interneurons in the spinal cord. Two logically related methods may be used to determine the site of change. The rationale of the method is to determine whether there is a change in the first millisecond bin of the excitatory peak of the PSTH of a discharging SMU, or a change in the amount of facilitation of the H-reflex in the first millisecond of facilitation following a conditioning stimulus (Hultborn et al., 1987; Fournier et al., 1986; Nielsen and Kagimara, 1993a; Nielsen et al., 1993b; Nielsen and Petersen, 1995). The method, therefore, exploits the monosynaptic component of the corticospinal connection, which has been clearly demonstrated for all muscle groups investigated in humans, whether in the upper limb (see the review by Mills, 1991), or in the lower limb (Brouwer and Ashby, 1992; Nielsen et al., 1993b; Devanne et al., 1997). A change in the amount of facilitation in the first millisecond of either type of record almost certainly reflects a change in synaptic transmission in the monosynaptic component of the pathway. Additionally, however, the measurements must be made for each task at the same level of background motor activity; and as discussed it would also be helpful to know the operating point on the input–output curves at which the measurements are made.

The last issue that will be dealt with in this section has to do with the detection of cross-talk artifacts in EMG recordings which is particularly important in the context of stimulation studies of the motor cortex. For example, this can help decide whether the brain stimulus produces co-activation of antagonist muscles, or reciprocal activation. This issue is particularly important in studies of neurological patients since reorganizations of the motor cortex may occur (Kew et al., 1994; Levy et al., 1990; Pascual-Leone et al., 1993). This technical matter is closely related to the question of what is activated by the brain stimulus, as opposed to how the brain is activated. The effect observed following stimulation at a given site over the motor cortex strongly depends on the existing level of background motor activity. In fact the effect can be reversed by switching motor activity from agonists to antagonists (Fig. 6). In this subject the center of a coned coil was placed just lateral to the vertex, which is nominally the 'ankle area' of the human motor cortex situated in the upper bank and within the paracentral lobule (Penfield and Rasmussen, 1950). Stimulation at this site during quiet produced a small response in the soleus. With the coil in the same position when the subject

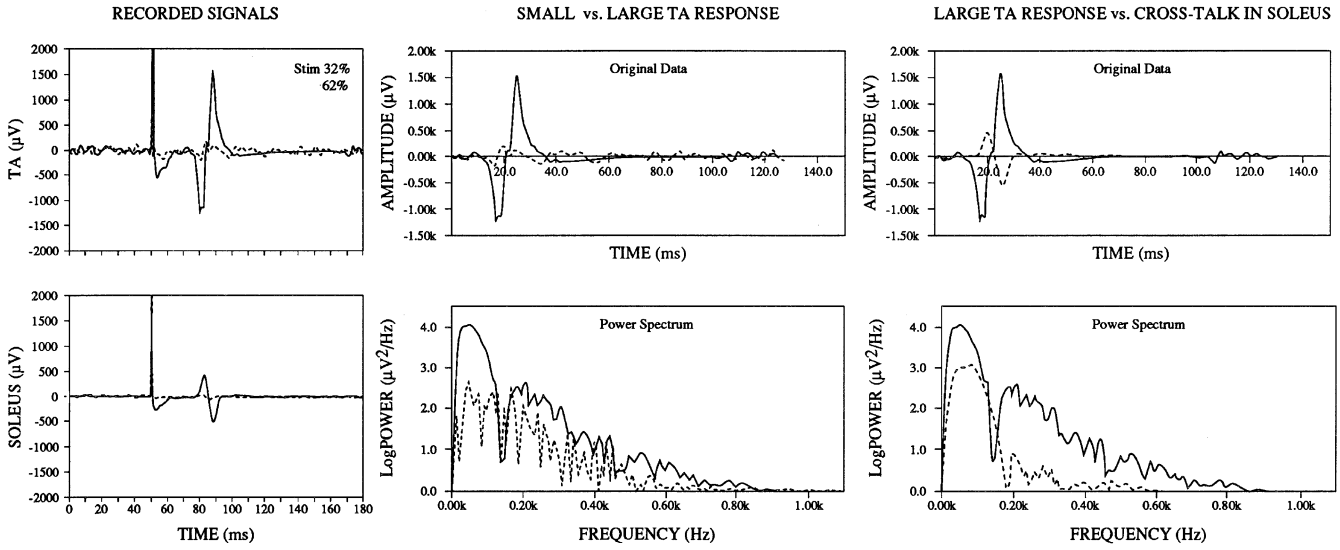

Fig. 7. The TA responses shown on the left were obtained during a small tonic voluntary contraction of the TA at two different stimulus intensities. The stimulus of 32% was near threshold, the one at 62% was near maximal. Note the small and smooth signals simultaneously recorded by the soleus electrodes. These signals are cross-talk artifacts as shown in the power spectra. The power spectra of a small or large EMRs have a similar frequency content (graphs in the middle). Whereas, when TA EMR is compared to the signal simultaneously recorded by the soleus electrodes (which is in this case larger than the small TA EMR), it is seen that the power spectrum of the soleus signal is shifted to the left, at lower frequencies. Note the logarithmic amplitude scale on the power spectra (graphs on the right).

leaned forward, thus requiring increased ankle extensor activity, the soleus EMR increased in amplitude. Conversely, when the subject leaned backwards, thus requiring increased ankle flexor activity, the TA was strongly activated. The small and smooth signals observable in the EMG recordings of the inactive antagonist muscle shown in Figs. 6 and 7 are cross-talk artifacts, not real EMG signals reflecting muscle activation. This conclusion is based on the following criteria illustrated in Fig. 7; (i) the signal power is much smaller than that of the simultaneously recorded signal over the active muscle, (ii) more importantly, the frequency content is narrower being shifted to the left, at lower frequencies of the power spectrum, (iii) the cross-talk signal is cross-correlated with the real EMG signal. The narrower and lower frequency content of cross-talk artifacts and their smaller power reflect the fact that they are produced by distant signals which are attenuated and filtered as they traverse the tissues (Lindström and Petersen, 1993). The cross-correlation of the real signal and the cross-talk signal, which in the case of distinct nearly synchronous peaks such as EMRs and H-reflexes is evident on inspection of the records—simply reflects the fact that the real signal is the cause of the cross-talk artifact. Finally, the simple expedient of muscle palpation will help corroborate the interpretation of the recorded signals, except for near threshold stimuli. Similar considerations apply to studies dealing with the H-reflex in which cross-talk artifacts are readily observed (Hutton et al., 1988).

To what extent the effect of a cortical stimulus depends on the level of cortical excitability at the moment of stimulation remains a matter of current debate (see details in, Amassian et al., 1987; Edgley et al., 1990; Burke et al., 1993; Baker et al., 1994; Mazzocchio et al., 1994). But what is clear is that the overtly observed response following stimulation of the same site over the motor cortex depends on which muscle is active at the time of the stimulus (Fig. 6). This implies that due consideration must be given to the excitatory and inhibitory bias at the segmental level. Therefore, studies of motor cortical task dependence should be done on the same muscle group activated in the same synergy in the different tasks investigated (e.g., reciprocally) and the measurements made at matched levels of motor activity. By matching the background level of motor activity in the different tasks, any change of the test response, such as the EMR or the H-reflex, must be due to a site presynaptic to the α-motoneurons. The site of change can be determined by the methods described above. On the other hand, studies involving comparing cortical control in different synergies (i.e., reciprocal activation vs. co-contraction) cannot lead to unequivocal conclusions (Iles and Pisini, 1992; Nielsen et al., 1993b; Nielsen and Petersen, 1995). The induced corticospinal volley may contain the same mixture of excitatory and inhibitory signals, regardless of task, whose overt expression simply reflect the excitability at the segmental level. Alternatively, the cortical elements may not be the same in the various synergies, nor the neuronal elements activated at the segmental

level (e.g., the input to IaIns). In either case, conclusions about differential cortical control cannot be definitive.

2.5. Recording the activity of SMUs and interpretation of the PSTH

This method will be dealt with in detail in other papers in this issue, but a few additional points pertinent to the presently discussed methods are worth mentioning. PSTHs are a very effective method for revealing monosynaptic connections. However, monosynaptic connections tend to be quite powerful, as a result the rebound which follows the initial short-latency excitatory peak may obscure weaker responses of longer latency (see in the Appendix in Capaday et al., 1990). On the other hand, longer-latency responses which are powerful enough, such as the M2 stretch reflex response, do clearly show up along with short-latency responses in PSTHs of SMUs (Calancie and Bawa, 1985). Thus, the method is useful for determining the relative potency of monosynaptic versus longer-latency components in a motor pathway.

The idea of varying the stimulus intensity, so as to generate complete input–output curves for a given pathway, is also applicable to single motor unit recordings. For example, in the recent study of Devanne et al., 1995, 1997 it was determined that the non-linear input–output relation of the corticospinal pathway as a whole was not due to the input–output properties of single α-motoneurons, since the discharge probability of single motor units increased linearly with stimulus intensity. Finally, with the advent of sophisticated adaptive waveform recognition systems (Miles et al., 1989) this type of experiment is made easier. Such systems even allow for SMU recordings in freely moving conditions, such as walking (De Serres et al., 1995).

3. Discussion

Two closely related ideas have been emphasized for all methods described herein—the influence of the background level of motor activity on input–output properties and the operating point on the input–output curves at which the experimental variable is measured. The reason why these matter is that the input–output properties of the neural pathways and the nature of the measurements themselves (e.g., extracellular recordings) are nonlinear; including the gain change of the input–output relation with the level of motor activity. Otherwise, the background level of motor activity, the size of the measured test response, or the operating point at which measurements are made would not matter. Despite this complication, it is relatively easy to understand and predict the outcome of these sorts of experiments by considering a simple model that is comprehensible in geometric terms. The model is neither dynamic nor does it embody, implicitly or explicitly, the underlying neural mechanisms. It is simply an empirical model, a curve fitting to experimental data that serves a heuristic purpose.

3.1. A simple model of input–output properties

The sigmoidal nature of the input–output relation described above for the corticospinal pathway (Figs. 6 and 7) also holds for the monosynaptic reflex pathway of the cat (Rall, 1955; Hunt, 1955) and similarly in man, as is evident from the early portion of H-reflex recruitment curves (Fig. 1, see also Crone et al., 1990). The Boltzmann sigmoidal function was found to be a useful fit to the experimental data, since it always accounted for at least 80% of the total variance (i.e., $R^2 \geq 0.8$). The parameters of this equation were calculated by the Levenberg-Marquard non-linear least-mean-squares algorithm (Press et al., 1986) and is available in a number of scientific software packages. This function is used, for example, to describe activation and inactivation of ionic conductances as a function of membrane potential. The Boltzmann function relating the amplitude of the response (R) and the stimulus intensity (S) is given by the following equation:

$$R(S) = \frac{R_{\max}}{1 + \exp[(S50 - S)/K]} \quad (1)$$

This equation has three parameters, the maximum value ($R_{\max}$) or plateau of the relation, the stimulus intensity (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 S_{50}. For example, halving the slope parameter doubles the steepness of the relation at S_{50}.

At the top of Fig. 8 four different sigmoidal curves based on the Boltzmann equation are shown to illustrate how the various parameters of this equation affect the form of the curve. Let's suppose that these curves represent the input–output properties of the monosynaptic reflex pathway in the spinal cord. The curve centered around a stimulus of 30% (i.e., $S_{50} = 30$) can be considered to be our reference, or control curve. Increasing the background level of motor activity shifts the curve to the left (Hunt, 1955; Rall, 1955), thus decreasing the S_{50} parameter. Tonic postsynaptic inhibition of the motorneurons would shift the curve to the right, and if intense enough would also decrease the plateau (Hunt, 1955; Rall, 1955). The steeper curve in Fig. 8 results from a decrease of the slope parameter K and its shift to the left centered around a stimulus of 20%—means that the level of motor activity is in-

creased relative to the control curve. Finally, to represent a tonic increase of presynaptic inhibition of the input pathway (e.g., Ia-afferent terminals) the response is scaled down by a multiplicative factor, producing a curve with a lower plateau and decreased slope.

The non-linear nature of these relations and especially the change in steepness which occurs as the background level of motor activity is increased have important methodological implications. For example, it has been suggested that for monosynaptic reflexes there is a range of test reflex amplitudes over which the amount of change produced by an added conditioning stimulus is constant (Crone et al., 1990). This is clearly inconsistent with a sigmoidal input–output relation since the first derivative of such a function is bell-shaped. As can be seen at the bottom of Fig. 8 there is

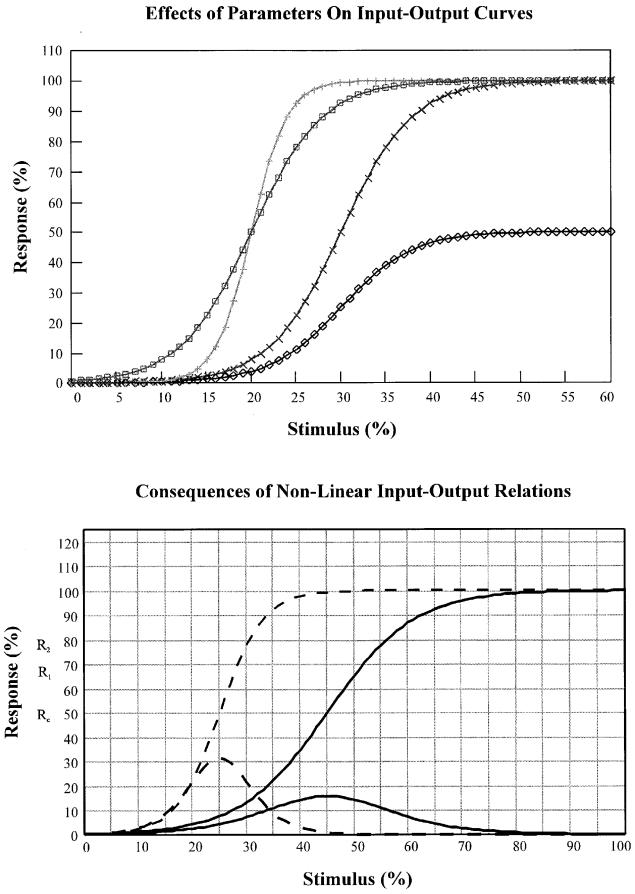

Fig. 8. The graph at the top of the figure illustrates how changing the parameters of the Boltzmann equation changes the shape of the sigmoidal input-output curve. Explanations of the various curves are given in the text. The graph at the bottom of the figure illustrates that the amount of change of a test response produced by an added conditioning stimulus depends not only on the amplitude of the test response itself, but also on the steepness of the curve at the test response. 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 of stimulus intensity.

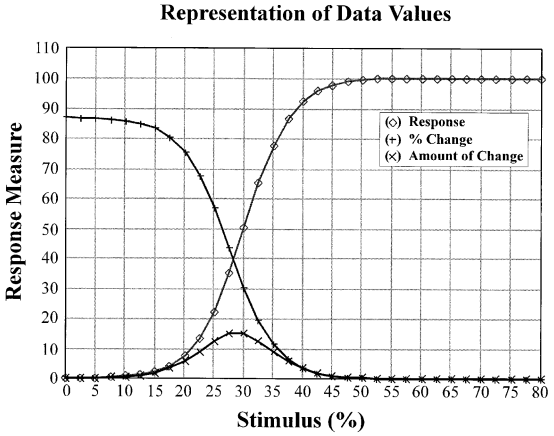

Fig. 9. The three curves on this graph are the sigmoidal input-output response, the percent change function and the amount of change function. The latter two functions were calculated for a conditioning stimulus of 2.5% added to each test stimulus. For inhibitory conditioning inputs the percent change and the amount of change functions would be mirror images, about the x-axis, of the curves shown here. Further details are given in the text.

no plateau level on such a relation. However, if small conditioning stimuli are used the differential function will have a relatively flat peak, which could be interpreted as a plateau when dealing with inherently variable experimental data. A runs statistical test may be done to determine whether the input–output curve at the operating point at which measurements are made is linear, or departs from linearity (Bendat and Piersol, 1986). More importantly, the increase of slope of the relation as a function of the level of motor activity means that the system can operate on different input–output curves. This implies that the amount of facilitation or inhibition produced by an added conditioning stimulus will depend on the level of motor activity. In the graphical example shown in Fig. 8 the dashed input–output curve at its steepest portion has a slope twice as great as the other curve. For each curve the differential function, which approximates the change of output expected for a small change of input, was calculated. Thus, for example, starting at a stimulus level which produces, in each case, a response of 50% (indicated as R_c on the graph), an 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 of the background activity on EMR or H-reflex amplitude is not a valid procedure to insure that the amount of facilitation or inhibition be independent of the test response amplitude (Hultborn et al., 1987; Crone et al., 1990). It is, therefore, important in experiments investigating neurophysiological mechanisms of human motor control to determine on input–output relation the system is operating in each

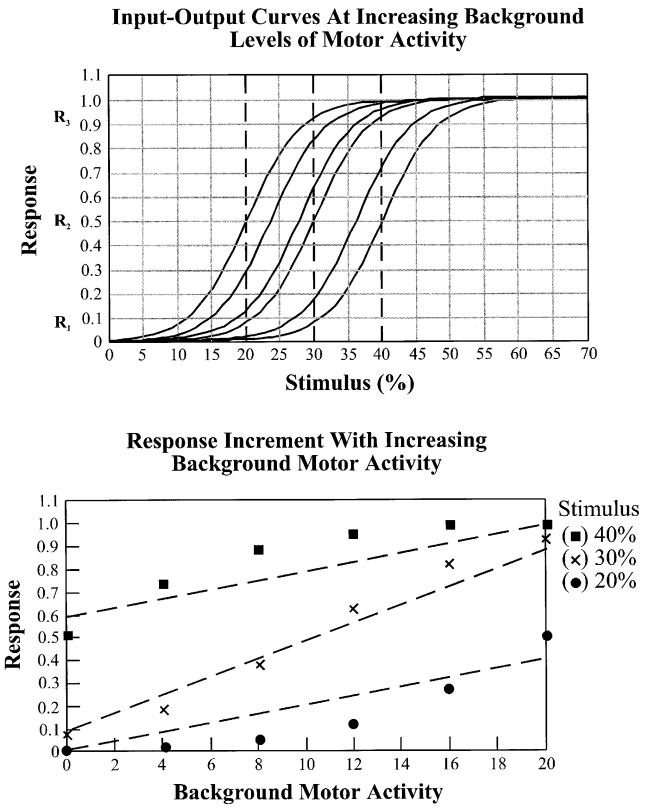

Fig. 10. This figures illustrates that the response increment with increasing levels of motor activity depends on the size of the initial test response (i.e. the response at nominally zero background activity). The background motor activity in the lower graph was calculated from the S_{50} parameters of the input-output curves above in such a way as to simulate the mean value of the rectified EMG signal. The main point illustrated here is that very small and very large responses (e.g. H-reflexes) increase relatively slowly with the background level of motor activity, whereas intermediate size responses increase much more rapidly.

task and at each intensity level of a task. This is an important consideration for all methods described in this article.

A further consequence of the nonlinear input–output relation is that the percent change of a control response—produced by a conditioning stimulus or by a task dependent change of input–output properties—depends on the size of the control response itself (Fig. 9). This idea has been expressed in different ways, mostly implicitly, by several authors (Hunt, 1955; Kuno, 1959; Paillard, 1955; Landau and Clare, 1964; Gassel and Diamantopoulos, 1964; Meinck, 1980). Direct experimental evidence was obtained in a more recent and detailed study of the issue by Crone et al. (1990). However, this is essentially a numerical fact; the sigmoidal input–output property makes it that—for a fixed amount of excitation or inhibition—the percent change for small test responses is very large and decreases as one gets closer to the plateau of the relation (Fig. 9). Data presented in this way be misleading; since they can be interpreted as demonstrating that small reflexes are more sensitive to excitation and inhibition. This is clearly not so, sensitivity is related to the first derivative of the input–output curve, not to the percent change function. It is clear from the above, that there is no mathematically sound way to compare responses, whether reflexes or EMRs, of widely different size. This is why previous authors (Hultborn et al., 1987; Crone et al., 1990) have suggested making comparisons on test responses of the same size. But, as we saw above, test responses of equal size may lay on input–output curves of different steepness. To what extent the bell-shaped function representing the amount of change reflects underlying neural quantities such as the number of motoneurons recruited or de-recruited is not known. No explicit model relating extracellular recordings to neural quantities has yet been fully developed. Further elaborations of recent models of input–output properties of motoneuron pools should provide an answer to this question (Capaday and Stein, 1987b; Fuglevand et al., 1993; Heckman, 1994; Slot and Sinkjaer, 1994).

Finally, the sigmoidal shape of the input–output function also helps explain how a test response increases with the background level of motor activity. In Fig. 10 six input–output curves measured at six different background activation levels are shown; the curves are simply shifted versions of each other (i.e., the S_{50} was varied). The data points in the bottom graph are obtained from the intersection of the dashed vertical lines with the sigmoidal curves in the top graph. For example, a stimulus of 30% will produce the steepest response increment as a function of the activation level. With increasing activation the response increases from R_1 to R_2, and further from R_2 to R_3 as shown in Fig. 10. A straight line was drawn through each set of data points to make the average steepness of the response at each stimulus intensity more apparent. It is clear that for weak stimuli near the foot of the relation, or for strong stimuli near the plateau of the relation, the responses will increase on average much less with the background level of motor activity. Thus, small and large responses grow relatively slowly with increasing background activity compared to test responses of intermediate size (Fig. 10, bottom). In summary, the present graphical analysis should help predict and interpret the outcome of these types of experiments.

3.2. Epilogue

The methods described in this article are used to measure changes in the input–output properties of various neural circuits involved in motor activity. The implicit assumption, or working hypothesis, behind this approach is that these changes serve to adapt the motor system to the biomechanical exigencies of the task (Stein and Capaday, 1988). There have been relatively

few direct attempts at relating neurophysiological changes to biomechanical changes, but this has now begun in human (Yang et al., 1991) and animal experiments (Nichols, 1994; Capaday, 1995).

Acknowledgements

This work was supported by the MRC of Canada. A contribution from the Rick Hansen Man in Motion Legacy Fund is also acknowledged. Charles Capaday is a research scholar of the Fond de la Recherche en Santé du Québec (FRSQ). The useful suggestions of Drs F.W.J Cody, M. Deschênes and F. Filion on a draft of the manuscript are gratefully acknowledged. I thank Dr H. Devanne, Ms B.A. Lavoie, Ms L. Bertrand and Mr François Comeau for their expert and dedicated participation in various aspects of this work.

Appendix A. Appendix 1

Electrical stimulation of nerve fibres of different diameters

The strength–duration equation, derived from experimental work going back to Lapique (1926), is useful for understanding how the duration of a stimulus is related to selective stimulation of nerve fibres of different diameters. The form of the strength–duration equation using the exponential function is useful for the present discussion (Woodbury, 1965). The equation relates the threshold stimulus intensity (S_{th}) required to activate a nerve fibre of a given time constant (τ_{m}) to the stimulus duration (d):

$$S_{th} = \frac{R_h}{1 - \exp(-d/\tau_m)} \quad (2)$$

The parameter R_{h} is the rheobase, or the stimulus intensity for a pulse of very long duration. It is the theoretical minimum stimulus intensity. A different form of this equation may be found in Ranck (1979). Either form of the equation embodies the experimental observation that as the pulse duration is shortened the required stimulus intensity increases.

The larger the fibre the smaller the membrane time constant. With this information it can be deduced that for a stimulus whose duration is much longer than $\tau_{\text{m}}(d \gg \tau_{\text{m}})$, $S_{\text{th}} = R_{\text{h}}$. Thus, fibres with the lowest threshold will be activated by weaker stimuli. More interestingly, for very brief stimuli ($d < \tau_{\text{m}}$) we obtain the following relation after using the series expansion of the exponential function near zero (i.e., $\exp(-x) = 1 - x$, for x values near zero):

$$S_{th} = R_h \frac{\tau_m}{d} \quad (3)$$

Which means that for brief stimuli the threshold stimulus intensity is proportional to the fibre's time constant, or equivalently its diameter. In summary, as Mortimer (1981) puts it 'One may achieve a greater degree of selectivity with shorter pulse widths (i.e., excitation of larger fibres without excitation of small fibres in the same physical space)'. However, it should be kept in mind that this conclusion holds only when the neural elements are approximately equidistant to the stimulating electrode. If small fibres are much closer to the stimulating electrodes than larger ones they will be stimulated first. The reader is referred to the chapter by Mortimer (1981) for a graphical presentation of the above principles.

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