Studies on the Corticospinal Control of Human Walking. I. Responses to Focal Transcranial Magnetic Stimulation of the Motor Cortex

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Capaday, Charles, Brigitte A. Lavoie, Hugues Barbeau, Cyril Schneider, and Mireille Bonnard. Studies on the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *J. Neurophysiol.* 81: 129–139, 1999. Experiments were done to determine the extent to which the corticospinal tract is linked with the segmental motor circuits controlling ankle flexors and extensors during human walking compared with voluntary motor tasks requiring attention to the level of motor activity. The motor cortex was activated transcranially using a focal magnetic stimulation coil. For each subject, the entire input-output (I-O) curve [i.e., the integral of the motor evoked-potential (MEP) versus stimulus strength] was measured during a prescribed tonic voluntary contraction of either the tibialis anterior (TA) or the soleus. Similarly, I-O curves were measured in the early part of the swing phase, or in the early part of the stance phase of walking. The I-O data points were fitted by the Boltzmann sigmoidal function, which accounted for ≥80% of total data variance. There was no statistically significant difference between the I-O curves of the TA measured during voluntary ankle dorsiflexion or during the swing phase of walking, at matched levels of background electromyographic (EMG) activity. Additionally, there was no significant difference in the relation between the coefficient of variation and the amplitude of the MEPs measured in each task, respectively. In comparison, during the stance phase of walking the soleus MEPs were reduced on average by 26% compared with their size during voluntary ankle plantarflexion. Furthermore, during stance the MEPs in the inactive TA were enhanced relative to their size during voluntary ankle plantarflexion and in four of six subjects the TA MEPs were larger than those of the soleus. Finally, stimulation of the motor cortex at various phases of the step cycle did not reset the cycle. The time of the next step occurred at the expected moment, as determined from the phase-resetting curve. One interpretation of this result is that the motor cortex may not be part of the central neural system involved in timing the motor bursts during the step cycle. We suggest that during walking the corticospinal tract is more closely linked with the segmental motor circuits controlling the flexor, TA, than it is with those controlling the extensor, soleus. However, during voluntary tasks requiring attention to the level of motor activity, it is equally linked with the segmental motor circuits of ankle flexors or extensors.

INTRODUCTION

Most of our knowledge on motor cortical function in humans and other primates is related to discrete movements of the digits or arm (e.g., Lemon 1995). On the other hand,

most of our knowledge on the role of the motor cortex in the control of locomotion comes from experiments in the cat (Armstrong 1986; Drew 1991). Little is known about the suprasegmental control of human walking and in particular the role of the motor cortex. In contrast, the biomechanical aspects of normal human walking are well characterized (Whittle 1996; Winter 1991), and considerable progress has been made in understanding segmental reflex activity (e.g., Lavoie et al. 1997; Stein and Capaday 1988; Yang and Stein 1990). There is thus a need to further our understanding of the role of the motor cortex during human walking.

In humans, strokes involving appropriate regions of the sensorimotor cortex or the internal capsule produce walking deficits. Among these is foot-drop, which results from decreased activation of the tibialis anterior (TA) and increased tonus in the ankle extensors (e.g., Conrad et al. 1985; Knutsson and Richards 1979). In the former study, 85% of the hemiparetic patients had less than half the normal level of motor output in the TA, with either normal or exaggerated ankle extensor activity. What the role of these sensorimotor regions in the control of human walking may be is not clear from this clinical observation alone, but it is clear that such lesions result in serious walking deficits that need explanation. In cats, who show little long-term locomotor deficits after lesions of the motor cortex unless challenged to walk over difficult terrain, such as across the steps of a horizontal ladder, the motor cortex is clearly active throughout the step cycle, but more so during the swing phase (e.g., Armstrong and Drew 1984; Drew 1991). The biomechanical exigencies of an erect bipedal gait pattern may have further encephalized the neural control of human walking. For example, the swing phase of human walking is a critical gait event that requires fine control (Lavoie et al. 1997).

The purpose of this study was to determine the extent to which the motor cortex, via the corticospinal tract, is linked with the segmental motor circuits of the ankle flexors and extensors during walking. The principle of the method we used to investigate this problem was to measure the whole of the input-output (I-O) curve (stimulus-response) in each task. This approach is novel and is a refinement of our preliminary study on the role of the motor cortex during voluntary versus postural activities (Lavoie et al. 1995). None of the previous studies of cortical task dependence were based on an explicit and detailed analysis of the I-O properties of the corticospinal pathway (e.g., Abbruzzese et al. 1994; Datta et al. 1989; Flament et al. 1993; Lemon et al. 1995).

The method, outlined in detail in the next section, allows one to determine the relative involvement of the corticospinal pathway in various motor tasks based on quantitative estimates of the three parameters that characterize the I-O curve of this pathway: the threshold, the maximum slope, and the plateau value (Devanne et al. 1997). A clear demonstration of a task-dependent change requires that one or more of these parameters changes independently of the level of motor activity (Capaday 1997; Devanne et al. 1997). A short account of some of the present findings was published as an abstract (Capaday et al. 1996).

METHODS

This study was done on 20 healthy human subjects ranging in age between 22 and 45 yr. Each subject was studied in a single session during walking (stance or swing phase) and during a voluntary task requiring attention to the level of motor activity (tonic ankle dorsiflexion or plantarflexion). In some subjects focal magnetic stimulation of the motor cortex was applied in several phases of the step cycle to determine the phase-resetting curve. The exact number of subjects studied in each task is given in the appropriate part of the RESULTS section. All subjects gave their consent after being informed of the nature and procedures of the experiments. The study was conducted in accordance with the declaration of Helsinki and approved by the local ethics committee.

Electromyographic recordings and magnetic stimulation

Bipolar electromyographic (EMG) recordings from the TA and soleus were obtained from pairs of surface Ag-AgCl disk electrodes (9-mm diam, 3-cm separation) placed over the belly of the muscle below the motor point. The electrodes were shielded right up to the recording surfaces and connected to an optically isolated, preamplifier by a shielded, twisted-pair cable, which reduces magnetic interference from the stimulating coil. The ground reference electrode 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, before digitizing at a rate of 5K samples/s. These signals were used to calculate the peak-to-peak value of the motor-evoked potentials (MEPs) and their coefficient of variation. The same EMG signals were also rectified and filtered (20 Hz to 1 kHz) before sampling by separate A/D channels. Spectral analysis was used for detection of cross-talk artifacts in the EMG recordings (Capaday 1997; Lindström and Petersen 1983).

Magnetic stimuli were applied over the scalp using a Cadwell MES-10 stimulator of maximum magnetic field strength of 2 Tesla, with a coned, double-D shaped, focal coil (16 cm × 8 cm). The MES-10 stimulator produces a damped, polyphasic electric field, about 200 μs in duration. The stimulus intensity was measured as a percentage of the maximum current that could be discharged through the coil. 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. The coil was placed parallel to and ~0.5- to 1.0-cm lateral to the midline and its center 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 (Devanne et al. 1997; Lavoie et al. 1995). 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 one of the experimenters, and its position and orientation were constantly checked to ensure that no slippage occurred during the experiment. These procedures have been shown to evoke stable and reproducible responses (Capaday 1997; Devanne et al. 1997; Lavoie et al. 1995). Further evidence is given in this paper.

Experimental procedures

The task order was randomized for each subject. For the voluntary tasks the subjects were seated with the tested leg slightly extended (knee at ~120° and ankle at ~30°) and the foot strapped onto a rigid support that allowed the subjects to dorsiflex or plantarflex the ankle nearly isometrically. The subjects were required to maintain a prescribed level of EMG activity in the soleus or TA, which was displayed on an analog meter. The interstimulus interval in the experiments involving tonic, voluntary activity varied randomly between 2 and 4 s. These intervals were used to minimize fatigue in these protracted experiments. Randomization tended to average out the effects of interstimulus interval on MEP amplitude. The required level of EMG activity for the TA was that generated during the early part of swing and for the soleus that generated during the early part of stance (Fig. 1). This protocol is identical to one of the protocols used in our recent study of the reciprocal inhibitory pathway (Lavoie et al. 1997). Typically, four responses were averaged at each stimulus strength. In some cases, eight responses were averaged at each stimulus intensity; this does not significantly decrease the standard error of the parameter estimates, but it does double the duration of the experiments. The procedure during walking was essentially similar, except that the stimulus was applied at a fixed time following heel contact so that it would produce a response either early in the stance phase or early in the swing phase (Fig. 1). Subjects walked at their own preferred speed (range 4.8–5.7 km/hr). Stimuli were applied randomly in one of five step cycles, with only one stimulus given per step. Note from the recordings shown in Fig. 1 that the stimuli were delivered during walking at times when the EMG activity of the respective muscle was nearly tonic. The rationale and limitations of the mean value of the rectified EMG as measure of the level of activity of a motoneuron pool have been discussed in detail in previous publications (Capaday 1997; Lavoie et al. 1997).

Measurement of I-O curves and rationale of the method

To measure the I-O curve of the corticospinal pathway of the soleus and TA in each task, the intensity of the stimulus to the motor cortex was increased in increments of 2% of the maximum stimulator output, and 4–8 MEPs were averaged at each stimulus intensity in real time. The level of motor activity just preceding a MEP was estimated from the mean value of the rectified surface EMG calculated over a 50-ms time segment just prior to the stimulus, or in the interval between the stimulus artifact and the response when the former was brief enough not to mask the EMG activity. This provides the best estimate of the level of ongoing activity at the moment a MEP is elicited. In this way, the whole of the I-O curve from threshold to saturation was obtained for each task at matched levels of EMG activity. The peak-to-peak value and integral of the averaged responses were calculated and plotted against the stimulus intensity. The Boltzmann sigmoidal function was fitted to the data points by the Levenberg–Marquard nonlinear, least-mean-squares algorithm (Press et al. 1986). This equation accounts for ≥80% of the total data variance (i.e., $R^2 \geq 0.8$) and is a significantly better fit to the data than a straight line (Devanne et al. 1997). The Boltzmann equation relating the amplitude of the response (MEP) and the stimulus intensity (S) is given by the following equation

$$\text{MEP}(S) = \frac{\text{MEP}_{\max}}{1 + \exp{[(S_{50} - S)/K]}} \qquad (1)$$

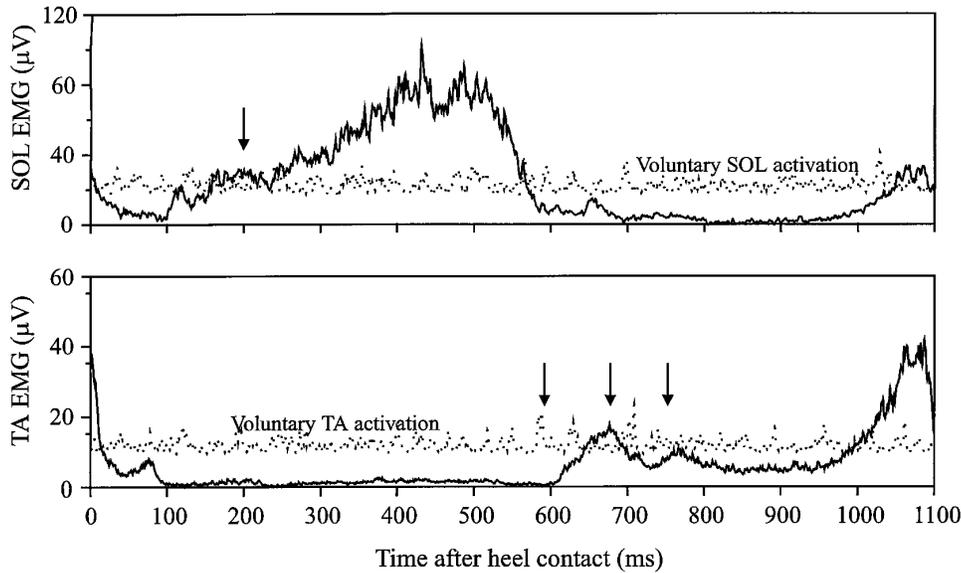This equation has the following three parameters: *1*) the maxi-

Time of Stimulation (↓) During Walking

FIG. 1. Example of the average ($n = $ 32 steps) electromyographic (EMG) activity of the soleus and tibialis anterior (TA) during the step cycle. Times at which motor cortex was stimulated are indicated by arrows. EMG activity during the voluntary dorsiflexion and plantarflexion tonic contractions are also shown. Note how closely the EMG levels are matched between tasks; note also that during walking the motor cortex was stimulated at times when the EMG activity of the respective muscle was nearly tonic. Stimulus applied just before TA burst near the 600-ms mark is at the transition from stance to swing, a time when the TA EMG is 0.

mum value (MEP_{max}) or plateau of the relation, *2*) the stimulus intensity (S_{50}) required to obtain a response 50% of the maximum, and *3*) 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}. The stimulus threshold is not an explicit parameter of *Eq. 1*, but changes of the threshold are directly related to the S_{50} parameter, as long as the slope of the relationship does not change. An alternative estimate of MEP threshold can be obtained by calculating the x-intercept of the regression line fitted to the rising section of the I-O curve (see Devanne et al. 1997).

From the foregoing it is clear that at a constant level of motor activity the threshold, maximal slope, and plateau value completely characterize the I-O relation of the corticospinal pathway in a given task. A clear demonstration of a task-dependent change would require, at least in part, that these parameters be shown to be statistically different at comparable levels of motor activity. Additional criteria and details are discussed in Capaday (1997). The method, however, does not explicitly allow one to determine, except at the level of the α-motoneurons, where within the corticospinal pathway the change(s) occurred, (e.g., intracortical circuits or segmental interneurons).

Data reduction and statistical analysis

Because there is no single general method, three different methods were used to determine task-dependent statistical differences between the I-O curves (Motulsky 1994). The first two methods determine whether there was a task-dependent difference at the level of a single subject. The simplest method, based on the standard error of estimate, determines by a *t*-test for correlated samples whether the best fit parameters (MEP_{max}, S_{50}, and K) differ between tasks. A more general approach, which considers the data sets as a whole, is to determine by an *F*-test whether fitting a curve for each data set significantly improves the total variance accounted for compared with fitting a single curve to all the data sets. The third method is an among subjects (i.e., across all repetitions of the experiment) comparison for each estimated parameter with the use of a *t*-test for correlated samples. The results of all three methods were consistent with each other, as will be described in the RESULTS.

Phase-resetting curves

To determine whether the motor cortex may be involved in the timing of the step cycle, classic phase-resetting experiments were done. The basic idea of this approach is that if a stimulus is applied to the mechanism producing an oscillation, the timing of the oscillation, or equivalently its phase, will be reset (e.g., Glass and Mackey 1988). This is easily understood in studies involving single neurons discharging repetitively and subjected to a depolarizing or hyperpolarizing pulse delivered intracellularly (e.g., Perkel and Mulloney 1974). The stimulus directly affects the timing mechanism (the balance and time course of excitatory and inhibitory conductances); consequently the time of a marker event, such as the peak of the action potential, is either advanced or delayed relative to the expected time. However, when stimulating a neuronal system such as the motor cortex, the situation is more complex but the essence of the logic is the same (Wagener and Colebatch 1996, 1997). If the motor cortex participates in the timing of the flexor or extensor EMG bursts during the step cycle, then a stimulus applied to it should change the duration of the step cycle in which the stimulus is applied and thus the time of occurrence of the next step. A complete phase-resetting curve was measured in four subjects in the following way. The phase of the stimulus (θ) is defined as a fraction of the step cycle t/T, where t is the time following heel contact when the stimulus is applied and T is the duration of the control step cycle estimated from the average of 32 steps just before beginning the stimulation protocol. We also verified that this estimate of the step cycle duration was not different from the one measured during the stimulation protocol, but from steps in which no stimuli were applied. This insured that the stimuli did not have an entraining effect on the step cycle. The phase of the stimulus was varied from zero to one, in steps of 0.2. The change of phase $\Delta\Phi$ was calculated by a standard formula

$$\Delta\Phi = \frac{(T - T_1)}{T} \qquad (2)$$

The phase response curve (PRC) is defined as the function relating the change of phase to the phase of the stimulus according to the following formula (e.g., Rinzel and Ermentrout 1989)

$$\Delta\Phi(\theta) = \frac{[T - T_1(\theta)]}{T} \qquad (3)$$
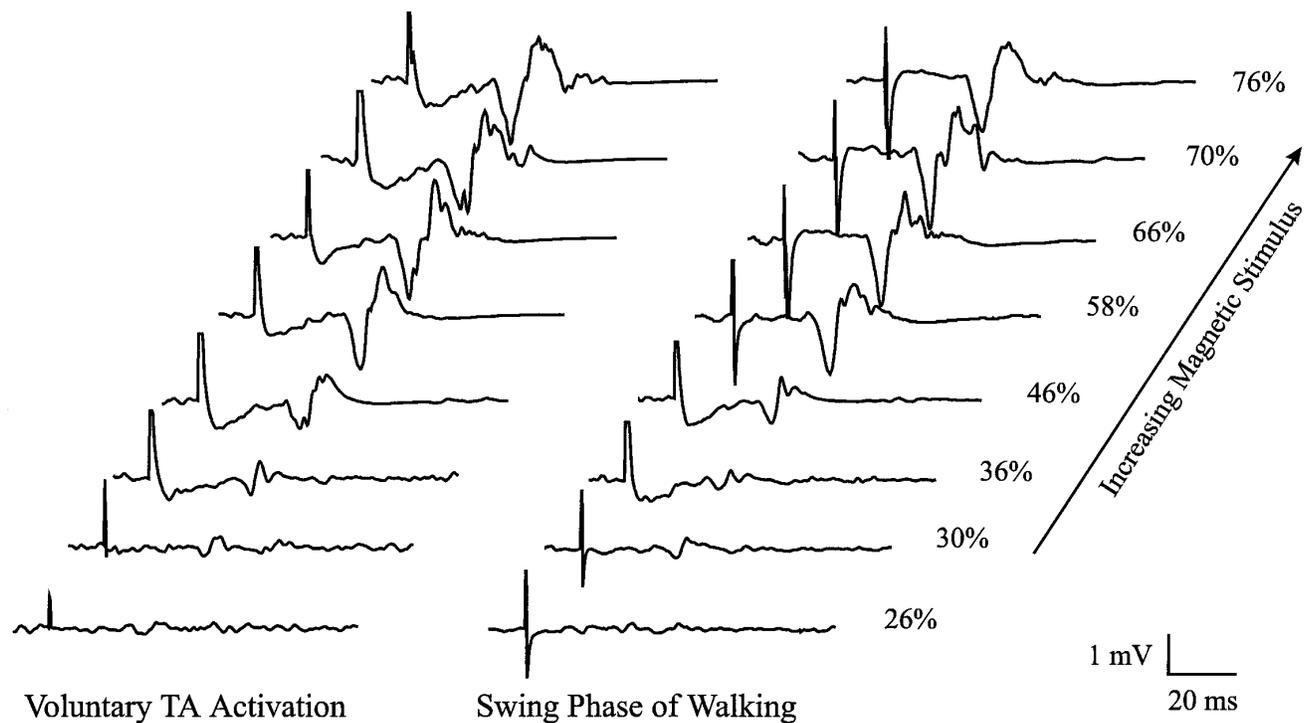
TA Motor Evoked Potentials

FIG. 2. Recordings of TA motor-evoked potentials (MEPs) during tonic voluntary TA activation (*left panel*) and during the swing phase of walking (*right panel*) evoked by increasing magnetic stimulus intensity, from threshold to supramaximal levels. Mean rectified TA background EMG was similar in both tasks [96 ± 8 (SD) μV and 98 ± 14 μV, for voluntary TA activation and the swing phase, respectively]. There was no activity in the soleus in either task. Magnetic stimuli were delivered at 845 ms after heel contact.

The PRC is simply a plot of $\Delta\Phi$ versus θ, from which a shortening or lengthening of the step cycle following a stimulus, i.e., a resetting of the step cycle, is readily apparent.

RESULTS

Three main observations were made in this study. In the first part of this section we show that the I-O curve of the TA obtained during voluntary dorsiflexion is statistically indistinguishable from the one obtained during the swing phase of walking. In the second section, we show that soleus MEPs attain a larger plateau value during voluntary plantarflexion than during the stance phase of walking. Additionally, TA responses are unexpectedly enhanced during the stance phase of walking compared with their size during voluntary plantarflexion. In the final section we show that stimulation of the motor cortex does not reset the step cycle.

I-O curves of the TA

Examples of TA MEPs, from threshold to maximum, evoked during tonic voluntary activity and during the swing phase of walking are shown in Fig. 2. Note the similarity in amplitude and waveform in the two tasks, indicating that the same group of motor units were recruited. Examples of I-O curves measured during voluntary dorsiflexion and during the swing phase of walking are shown in Fig. 3. The stimulus was delivered 150 ms after the onset of the TA EMG burst during swing. The same mean level of EMG

activity was maintained during voluntary dorsiflexion. As can be seen in the two examples shown in Fig. 3, there is no statistical difference between the I-O curves measured in the two tasks. In other words, fitting a curve to each data set does not significantly reduce the variance compared with fitting a single curve to all the data points. The data presented in Fig. 3 also address the issue of reproducibility of the I-O curves. Clearly, the fact that statistically indistinguishable curves were obtained in two kinetically different tasks shows that the measurements are reproducible. It may also be asked whether the data obtained during walking were more variable than those obtained during voluntary activity, thus possibly obscuring any potential difference. Figure 4 shows another example in which the I-O curves were measured from the peak-to-peak value of the MEPs, from which it is easy to calculate their coefficient of variation. The coefficient of variation is inversely related to the amplitude of the MEP, as can be seen in Fig. 4 (see also Devanne et al. 1997). There was, however, no statistical difference between the regression lines fitted to each data set. In other words, the MEPs were no more variable when elicited during the swing phase of walking than during tonic voluntary dorsiflexion. A among-subjects statistical comparison of the estimated I-O function parameters confirmed that there were no task-dependent differences. A covariance analysis of the relation between MEP latency or duration and MEP amplitude showed that there were no task-dependent differences in the latency or duration of the TA MEPs. Additionally,
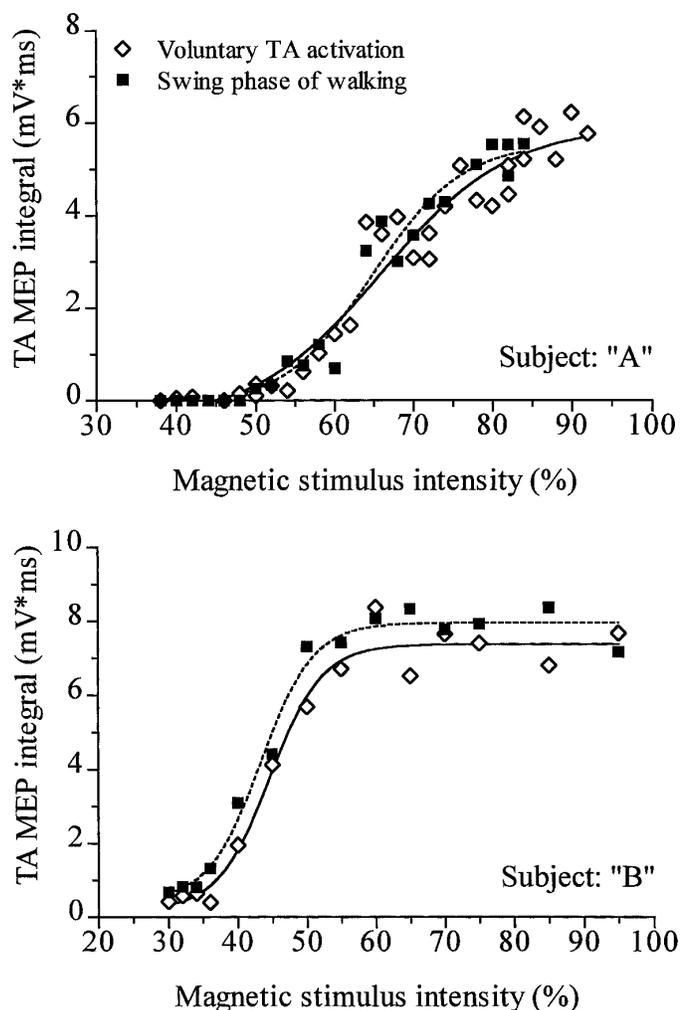
FIG. 3. Input-output (I-O) curves of TA MEP integrals measured during tonic voluntary TA activation and during the swing phase of walking in 2 different subjects. For each subject, the mean rectified TA EMG was similar in both tasks [*subject A*: 23 ± 3 (SD) μV and 27 ± 4 μV; *subject B*: 49 ± 6 μV and 43 ± 9 μV, for voluntary TA activation and swing phase, respectively]. There was no activity in the soleus in either task. Magnetic stimuli were delivered in the middle of the TA burst during the swing phase of walking at 850 and 655 ms after heel contact for *subjects A and B*, respectively. For *subject A*, the estimated I-O curve parameters during voluntary TA activation were 5.81 ± 0.33 mV·ms, plateau ± SE; 5.4 ± 0.1 mV·ms/%, max slope ± SE; 66.7 ± 1.4%, S_{50} ± SE; number of data points, 29. Those during swing phase of walking were: 5.66 ± 0.31 mV·ms, plateau ± SE; 6.6 ± 0.7 mV·ms/%, max slope ± SE; 65.4 ± 1.0%, S_{50} ± SE; number of points, 22. For *subject B*, the estimated I-O curve parameters during voluntary TA activation are 7.38 ± 0.22 mV·ms, plateau ± SE; 3.8 ± 1.0 mV·ms/%, max slope ± SE; 44.6 ± 1.1%, S_{50} ± SE; number of data points, 14. Those during swing phase of walking are 7.96 ± 0.45 mV·ms, plateau ± SE; 3.8 ± 0.8·mV ms/%, max slope ± SE; 43.4 ± 0.9%, S_{50} ± SE; number of data points, 14. For both subjects, no statistical differences were found between the parameters of I-O curves in each task ($P > 0.4$) or for the curves taken as a whole.

covariance analysis also showed that there was no task-dependent difference in the relation between silent period duration and MEP amplitude.

In six subjects we systematically explored responses at the transition from stance to swing, a phase of the step cycle during which important qualitative and quantitative changes may occur (e.g., Schubert et al. 1997). TA MEPs elicited just before the onset of TA activity and after the cessation

of extensor activity were smaller than those elicited during the period of flexor activity. Thus we found no evidence of enhanced TA MEPs at the transition from stance to swing. An example is shown in Fig. 5 for a stimulus of 62%, approximately equal to the S_{50} parameter estimate in this subject. The TA MEPs increase approximately linearly with the mean value of the TA EMG (Fig. 5). For a threshold stimulus, 52% in the example shown in Fig. 5, the response increases much more slowly as a function of the background EMG, as predicted by a simple model of I-O properties of the
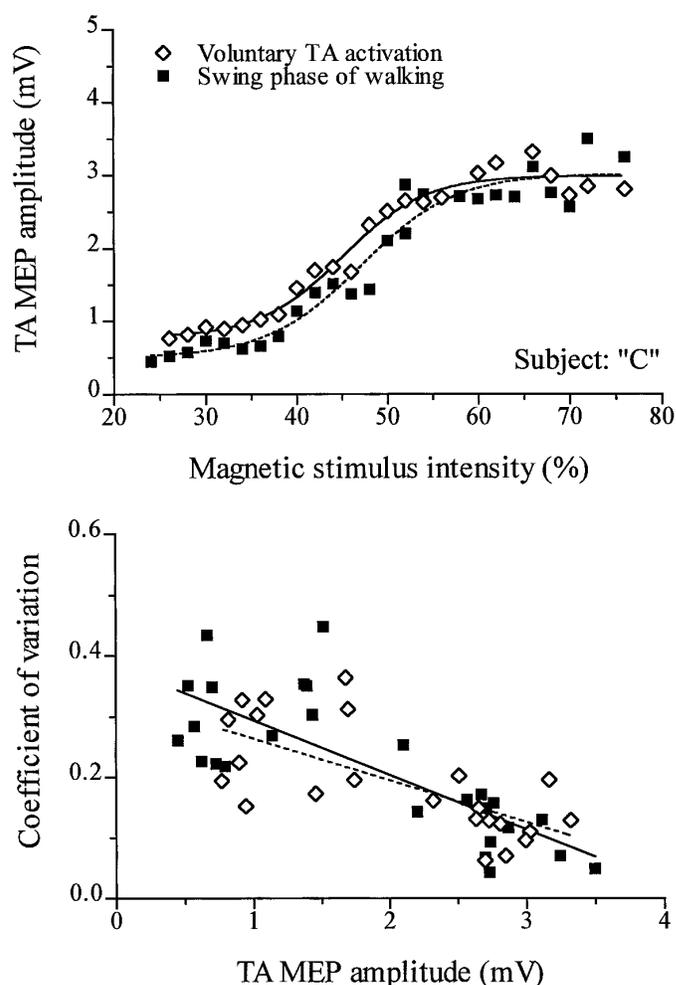

FIG. 4. I-O curves of TA MEP peak-to-peak amplitudes and the corresponding coefficient of variation measured during tonic voluntary TA activation and during the swing phase of walking for another subject (*subject C*). Mean rectified TA EMG is similar in both tasks [96 ± 8 (SD) μV and 98 ± 14 μV for voluntary TA activation and swing phase, respectively]. There was no activity in the soleus in either task. The magnetic stimuli were delivered at 845 ms after heel contact, which corresponds to the middle of the TA burst in the swing phase of walking. I-O curve parameters during voluntary TA activation were 2.99 ± 0.07 mV·ms. plateau ± SE; 4.6 ± 0.8 mV·ms/%, max slope ± SE; 45 ± 1%, S_{50} ± SE; number of data points, 23. Those during swing phase of walking were: 3.02 ± 0.12 mV·ms, plateau ± SE; 5.2 ± 1.2 mV·ms/%, slope ± SE; 47 ± 1%, S_{50} ± SE; number of data points, 26. No statistical differences were found between the parameters of the I-O curves for each task ($P > 0.1$) or for the curves taken as a whole. Coefficient of variation is inversely correlated to the amplitude of the TA MEP in both tasks. Equations are $y = -0.07x + 0.33$, $R^2 = 0.48$, $P = 0.0003$ for voluntary TA activation and $y = -0.09x + 0.38$, $R^2 = 0.61$, $P < 0.0001$ for swing phase of walking. Neither the slopes nor the y-intercepts were statistically different ($P > 0.3$).
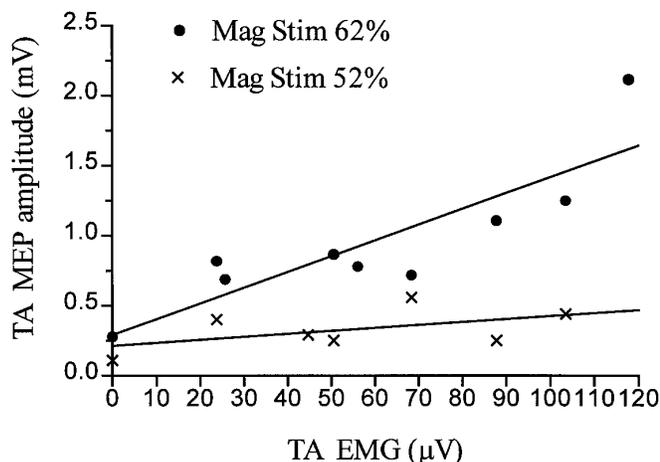
FIG. 5. Example of the relationship between the amplitude of TA MEPs and the mean value of the background level of TA EMG activity for 2 magnetic stimulus intensities. For a stimulus of 62%, approximately equal to the S_{50} value for this subject, the MEPs increased at a rate of 11.3 μV/ μV of background activity, the correlation coefficient (R) was equal to 0.86. For a stimulus of 52% approximately equal to the threshold during tonic activity the responses increased much more slowly 2.1 μV/μV of background activity, R was 0.51, but the correlation was not significantly different from 0. Difference in slopes was, however, highly statistically significant. Note that MEPs elicited at the transition from stance to swing, at a time when the soleus activity was terminated and the TA activity not yet begun (i.e., at 0 EMG activity), were clearly not the largest responses obtained.

motoneuron pool (Capaday 1997). The important point is that at neither stimulus intensity was the size of the MEP largest at the transition from stance to swing (i.e., at 0 TA EMG in Fig. 5), as suggested by Schubert et al. (1997).

I-O curves of the soleus

During tonic voluntary plantarflexion, stimulation of the motor cortex elicited MEPs in the soleus that increased sigmoidally with stimulus intensity (Fig. 6). Responses in the TA were either absent or very much smaller than those of the soleus (Figs. 6 and 7). During the stance phase of walking, on the other hand, the TA MEPs were the dominant responses in four of six subjects, despite the fact that during stance the TA is silent and the soleus active. An example of this striking result is shown in Fig. 6. The plateau value of the soleus I-O curve is ~45% smaller during stance than during voluntary plantarflexion and the TA MEPs larger than those of the soleus. Thus two separate phenomena were observed during the stance phase, an enhancement of the TA MEPs relative to their size during voluntary plantarflexion and a reduction of the soleus MEPs relative to their size during voluntary plantarflexion. Examples of recordings of soleus and TA MEPs during voluntary plantarflexion and during the stance phase of walking are shown in Fig. 7. Note the relatively large soleus MEPs and nearly absent TA MEPS during voluntary plantarflexion. In contrast, during the stance phase of walking the largest responses, by which we simply mean the absolute size of the potential, were observed in the TA and the soleus MEPs were clearly attenuated. The TA MEPs were not the largest responses during stance in all subjects, but in all they were enhanced relative to their amplitude during voluntary plan-

tarflexion. Similarly, in all subjects the soleus MEPs were reduced during the stance phase of walking relative to their size during voluntary plantarflexion. Of the three I-O parameters, the plateau value was the only one that differed statistically between tasks. In each subject, the reduction of the plateau value was statistically significant at a P value of ≥ 0.01. In addition to the S_{50} parameter as an estimate of MEP threshold, the threshold was also estimated from the regression line of the data points on the rising portion of the I-O curves. The average threshold estimated by this method was 41.8% (SD = 8.1%; n = 6 subjects) for the voluntary plantarflexion task and 41.3% (SD = 9.6%; n = 6) for the stance phase of walking. The difference between thresholds was not statistically significant (t-test, $P > 0.68$; n = 6 subjects). A summary of the results obtained in the stance phase are presented in Table 1. As was the case with the TA MEPs, a covariance analysis of the relation between soleus MEP latency or duration and MEP amplitude showed that there were no task-dependent differences in the latency or duration of the soleus MEPs. Additionally, covariance analysis also showed that there was no task-dependent difference in the relation between silent period duration and MEP amplitude.

Phase-resetting experiments

Regardless of the phase at which a stimulus was applied, or the stimulus intensity over the range used, the step cycle was not reset. An example of a PRC is shown in Fig. 8*A*. It is clear that no stimulus at any phase of the step cycle advanced or delayed the onset of the next cycle. The stimulus intensity used in the phase-resetting experiment shown in Fig. 8*A* was 60% of the maximum stimulator output. This stimulus produced obvious muscular contractions in the lower limb, but despite this the next step occurred at the expected time. It may be, however, that more intense stimuli are required to reset the human step cycle. Over the range of stimuli explored, up to 90% of stimulator output in some cases as in Fig. 8*B*, no phase shift was observed. In Fig. 8*B* the stimuli were delivered at the transition from stance to swing. The maximum stimulus intensities used in these experiments were limited to ones not producing a stumbling of the subject. Following a stumble, which we carefully avoided, the time of the next step would differ from the expected time, assuming that the subject continues to walk. But a stumbling reaction is a qualitative change in system behavior; that is, the subjects are not walking while they are stumbling. Such a qualitative change is akin to a transient bifurcation of system behavior and as such is not quantifiable by a PRC (e.g., Glass and Mackey 1988).

The PRC is measured from differences between control and perturbed step cycle durations. These are determined by the duration and timing of the locomotor bursts. However, the PRC measurements are not directly related to these underlying physiological variables. Thus in principle, many combinations of locomotor burst durations and timings may produce a step cycle of fixed duration. Shown in Fig. 9, the recordings of the soleus and TA EMG bursts during stimulation of the motor cortex at various phases of the step cycle demonstrate that neither the timing nor the duration of the EMG bursts was affected. The average EMG activity
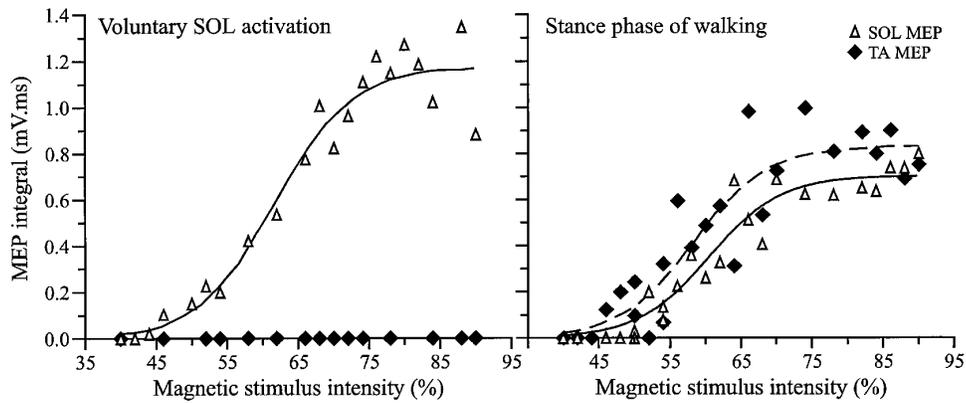
FIG. 6. I-O curves of soleus (SOL) and TA MEP integrals measured during tonic voluntary SOL activation and during the stance phase of walking. For each subject, the mean rectified SOL EMG was similar in both tasks [13.5 ± 2.3 (SD) μV and 8.6 ± 2.5 μV, for voluntary SOL activation and stance phase, respectively]. There was no activity in the TA in either task. Magnetic stimuli were delivered 200 ms after heel contact, which corresponds to the early part of the stance phase of walking. SOL I-O curve parameters during voluntary SOL activation were 1.18 ± 0.053 mV·ms, plateau ± SE; 5.5 ± 0.9 mV·ms%, max slope ± SE; 61.8 ± 1.2%, S_{50} ± SE; the number of data points is 22. Those during stance phase of walking were 0.703 ± 0.04 mV·ms, plateau ± SE; 5.1 ± 1.0 mV·ms%, max slope ± SE; 60.5 ± 1.3%, S_{50} ± SE; number of data points, 25. A statistical difference was found between the plateau parameters ($P < 0.0001$), but not between the max. slope and S_{50} parameters ($P > 0.4$). For that subject, no TA MEPs were recorded during voluntary SOL activation. TA I-O curve parameters during the stance phase of walking were 0.832 ± 0.062 mV·ms, plateau ± SE; 5.3 ± 1.4 mV·ms%, max slope ± SE; 58.3 ± 1.8%, S_{50} ± SE; number of data points, 25. In comparing the SOL and TA I-O curves obtained during stance, no statistical difference was found between the curve parameters ($P > 0.08$) or for the curves taken as a whole.

($n = 32$ steps) of the extensor and flexor are shown in the top of the figure, along with the waveforms representing ±SD about the mean. When the stimulus was applied in the stance phase, the duration of the soleus burst was not changed ($\theta = 0$, $\theta = 0.36$ in Fig. 9). Similarly, when the stimulus was applied at the transition from stance to swing ($\theta = 0.55$) the duration of the first TA burst remains the same as the control, despite a large MEP that occurred in the first part of the burst. That is, the TA burst ends near the 1,000-ms mark as expected. A stimulus delivered late in the step cycle ($\theta = 0.91$), at the time of the second TA burst, produced a large MEP in the TA that obscures the locomotor burst but does not affect the time of heel contact.

In summary, the main effect was simply the expected decrease of activity following a MEP, with the EMG activity resuming thereafter and terminating at the expected time.

DISCUSSION

This study dealt with activation of the corticospinal pathway taken as a whole, i.e., the motor cortical circuitry, segmental interneurons, and the α-motoneurons. Other corticofugal influences, such as motor cortical relays to brain stem nuclei, may also be involved, although the short latency MEPs we measured are probably mainly due to corticospinal transmission (e.g., Rothwell et al. 1997). Our perspective
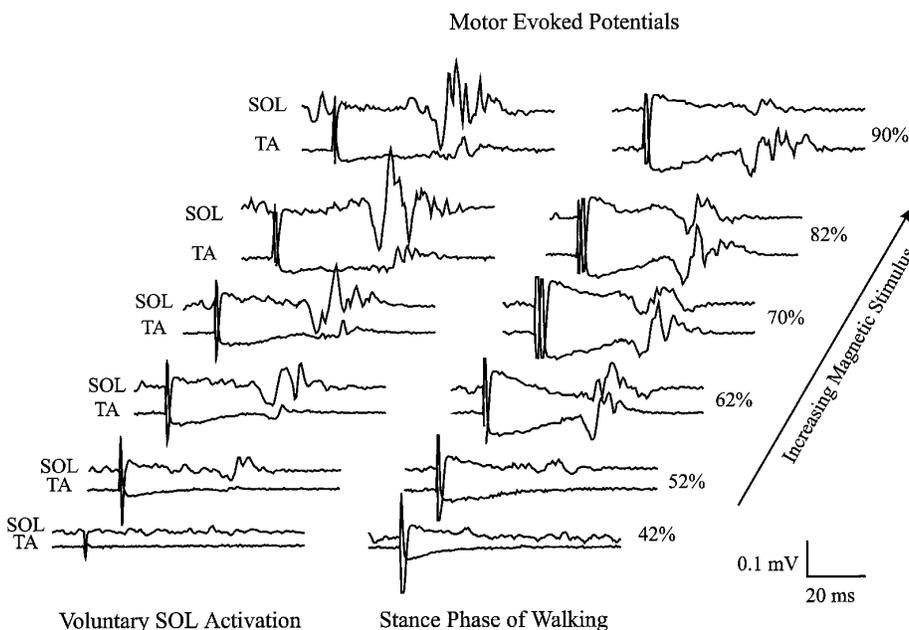

FIG. 7. Recordings of SOL and TA MEPs during tonic voluntary SOL activation (*left panel*) and during the stance phase of walking (*right panel*) evoked by increasing magnetic stimulus intensity, from threshold to supramaximal levels. Mean rectified SOL EMG is similar in both tasks [13.5 ± 2.3 (SD) μV and 8.6 ± 2.5 μV for voluntary SOL activation and stance, respectively]. There was no activity in the TA in either task. Magnetic stimuli were delivered at 200 ms after heel contact, which corresponds to the early part of the stance phase of walking.

TABLE 1. *Summary of observations during stance vs. voluntary plantarflexion*

Subject	Stance vs. Plantarflexion			Dominant Response	
	SOL MEPs	% decrease	TA MEPs	Stance phase	Vol. plantarflexion
1	Reduced	5	No TA	SOL	SOL
2	Reduced	29	Increased	TA	SOL
3	Reduced	28	Increased	TA	TA
4	Reduced	10	Increased	SOL	SOL
5	Reduced	40	Increased	TA	SOL
6	Reduced	43	Increased	TA	SOL

Six subjects were tested during voluntary (Vol) plantarflexion and during the stance phase of walking, each in the same experimental session. In *subject 1,* only soleus (SOL) motor-evoked potentials (MEPs) could be obtained during plantarflexion or the stance phase of walking. Tibialis anterior (TA) MEPs could not be elicited in this subject even during dorsiflexion. In *subject 3,* during voluntary plantarflexion soleus MEPs dominated at the lower stimulus intensities, but TA MEPs suddenly appear and dominate at higher stimulus intensities. Nonetheless, the soleus MEPs were reduced during the stance phase ($P < 0.01$) and the TA MEPs enhanced. The percent decrease column refers to the reduction of the plateau level during the stance phase compared to voluntary plantarflexion.

is that stimulation of the motor cortex elicits responses that depend on the excitability of several elements in the corticospinal pathway, as we have suggested in the past (Devanne et al. 1997). The results of the present experiments thus reflect in general terms the functional linkage between the motor cortex and the segmental circuits activated by the corticospinal tract. We have shown that during walking the corticospinal pathway is more closely linked to the ankle flexor TA than it is to the ankle extensor soleus. Furthermore, the corticospinal pathway is more closely linked to the TA not only during the swing phase, but also in the stance phase (Fig. 10). This is a remarkable result because during stance the soleus is active, but the TA is silent. An implication of this finding is that some other pathway(s), without excluding a contribution from the corticospinal pathway, may be responsible for excitation of the soleus.

Functional interpretation of the results obtained in the stance phase

It was suggested that part of the excitatory drive to the soleus α-motoneurons comes from the stretch reflex pathway (Stein and Capaday 1988), and it was later estimated that this pathway may contribute ~40–60% of the total (Yang et al. 1991). This may explain why the soleus MEPs are reduced during the stance phase of walking. However, the site of change within the corticospinal pathway cannot be determined on the basis of the present measurements. The results only demonstrate that the corticospinal pathway taken as a whole is less engaged during the stance phase of walking compared with voluntary tonic plantarflexion requiring attention to the level of motor activity. However, because the I-O measurements for each task were done at matched levels

of EMG activity, the site of change is unlikely to be at the level of the soleus α-motoneurons (see Capaday 1997; Lavoie et al. 1997). Elucidating the central origin of the excitatory drive to the ankle extensors during the stance phase of human walking will be an important and challenging endeavor.

It is important to note that the reduction of the plateau level would not have been observed had we not characterized the entire I-O relation of the corticospinal pathway to the soleus. Indeed, this observation was missed in the only other study of corticospinal control during human walking (Schubert et al. 1997). On the contrary, Schubert et al. reported that the MEPs recorded from the gastrocnemii were enhanced during the stance phase compared with voluntary activity. The discrepancy is unlikely to be due to differences between the soleus and the gastrocnemii. In untrained humans the gastrocnemii contain ~50% type S fibers (e.g., Ariano et al. 1973), and their EMG pattern during walking is very similar to that of the soleus. There are several other differences between our findings and those of Schubert et al. 1997. In our study the subjects adopted their own preferred cadence, whereas in the study of Schubert et al. (1997) subjects walked in synchrony to a metronome beat, which raises the possibility of a greater level of cortical involvement in their study. Schubert et al. (1997) used a round, nonfocal coil, which activates widespread areas of the motor cortex including the forelimb and hindlimb representations. The simultaneous activation of multiple representation areas has consequences that are difficult to predict. In the present study we measured complete I-O curves from threshold to saturation, whereas in the study of Schubert et al. (1997) only a single stimulus of 0.95 times the threshold during a weak contraction was used. Conclusions from such single
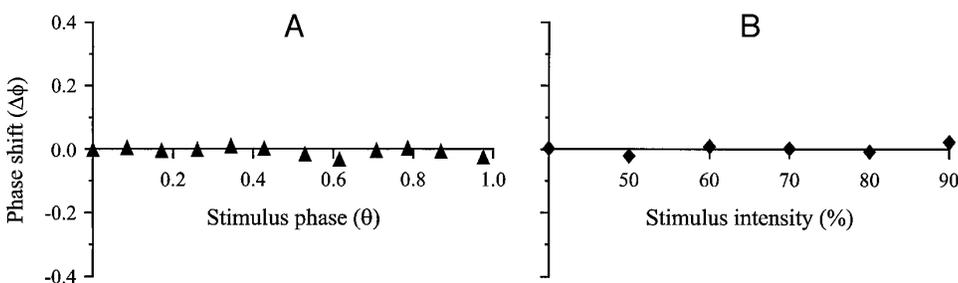

FIG. 8. Summary of results of the phase-resetting experiments in 1 subject. *A*: phase response curve (PRC) shows no phase shift ($\Delta\phi$) occurred at any stimulus phase (θ). Stimulus intensity was 60% of the maximum stimulator output. *B*: increasing the stimulus intensity (up to 90%) at the transition from stance to swing did not reset the step cycle either.
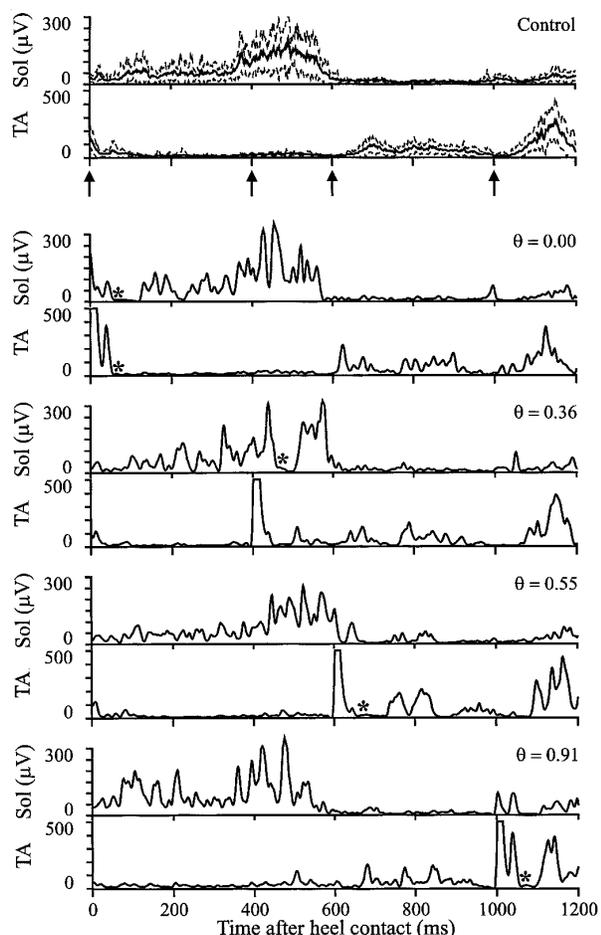
FIG. 9. Recordings of SOL and TA EMGs during normal walking and in steps in which the motor cortex was stimulated. First 2 graphs (*Control*) represent the mean SOL and TA EMG levels (average of 32 step cycles) in control step cycles. – – –, ±SD about the mean. Stimulus intensity was 60% of maximum stimulator output and delivered at various phases of the step cycle (↑). Four representative EMG traces obtained in single stimulated step cycles are shown labeled with the stimulus phase (θ). Single traces were smoothed with a digital low-pass filter with a cutoff at 20 Hz. Note that neither the onset nor duration of the EMG bursts is affected by the stimulus. Main effect was simply the expected decrease of activity following the MEP (*), with the EMG activity resuming thereafter and terminating at the expected time.

point measurements are limited. For example, not only was the reduction of the soleus MEPs missed in their study, but also the enhancement of the TA MEPs during the stance phase. Finally, the method of quantification of the MEPs used by that group leads to a distortion of the functional relationship between MEP size and the background level of motor activity. This relationship is approximately linear as shown in this study and in previous ones (e.g., Lavoie et al. 1995). In the study by Schubert et al. (1997) the MEP amplitude obtained during walking was divided by the background level of motor activity. This transforms a direct linear relationship into a nonlinear (hyperbolic), inverse relationship, meaning that MEPs obtained at low levels of background EMG activity are made to appear enhanced relative to those obtained at higher background levels. In fact with their analysis, MEPs obtained at zero or small background levels are made to appear ''infinitely'' facilitated. This may

well explain why Schubert et al. (1997) reported a large facilitation of the TA MEPs at the transition from stance to swing, whereas we have shown that this is not the case (Fig. 5).

Functional interpretation of the results obtained in the swing phase

The close link we found between the corticospinal pathway and the flexor TA is in agreement with the results of unit recordings from the cat motor cortex during normal walking (Drew 1991, 1993; Widajewicz et al. 1994). Most task-related neurons discharge in relation to flexor activity during normal feline walking and these, as well as newly recruited units, increase their discharge when the animal steps over an unexpected obstacle. However, the present results further our understanding of the issue in two main respects. We have shown that during voluntary ankle plantarflexion there is a demonstrable link between the corticospinal pathway and the neural circuits controlling the soleus, but during the stance phase of walking this functional link is attenuated. Reciprocally, the TA MEPs are enhanced during stance relative to their size during voluntary ankle plantarflexion (Fig. 10). The reduced activation of the TA in stroke patients during walking may thus be a consequence of decreased corticospinal influences. But we wish to make it clear that the nature of corticospinal control, e.g., phasic drive to the motoneurons or tonic influences on spinal interneurons, has not been determined by the present study and remains to be elucidated.

How can the reduction of the soleus MEPs and the enhancement of the TA MEPs during the stance phase be explained? One possibility is that during stance, motor cortical
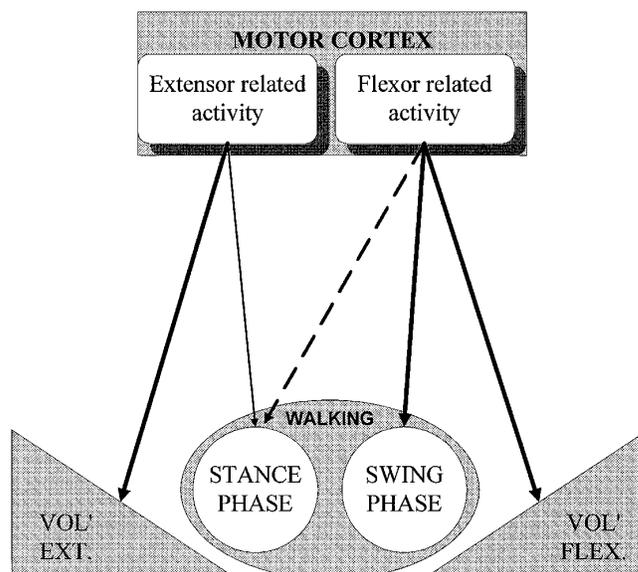

FIG. 10. Summary of strength of the link between the motor cortex, via the corticospinal tract, and the segmental neural circuits controlling the soleus and TA during voluntary activity compared with walking. Thickness of the arrows is proportional to the suggested strength of the link between the motor cortex and the segmental motor circuits in each case. Dashed arrow pointing from the flexor related motor cortical zone to the stance phase of walking is used to indicate that this was an unexpected result. Further details are given in the text.

activity related to the TA is greater than during voluntary plantarflexor activity. Consequently, the premotoneuronal excitatory interneurons will be more excitable and the TA α-motoneurons, although silent, will be closer to threshold. A second possibility is that during stance, motor cortical activity related to the ankle extensors is reduced compared with voluntary activity. This would account for the reduction of the soleus MEPs. The enhancement of the TA MEPs would result from the relatively lower motor cortical threshold for eliciting TA responses, together with perhaps a more depolarized membrane potential of the TA α-motoneurons. In any case, further experiments will be required to elucidate the mechanisms underlying this important observation on the neural mechanisms of human walking. From the functional point of view, the increased responsiveness of flexor motoneurons during stance may have to do with the necessity to quickly stop extensor activity and flex the limb in response to a nociceptive stimulus. It may also be related to the readiness to change direction as may be required. It is also interesting to consider that the TA is the earliest recruited leg muscle during compensatory postural reactions to slipping while walking (Tang et al. 1998).

Interpretation of the phase-resetting experiments

Given that the origin of motor activity during human walking is not known, we thought it interesting to attempt to determine whether the motor cortex may be part of the neural system involved in timing the locomotor bursts. The results of the phase-resetting experiments suggest that this is not the case. In no instance was the step cycle shortened (i.e., the swing phase precociously initiated) or lengthened (i.e., the stance phase lengthened). There are two points that need to be addressed on this issue.

First, do the conditions of the present experiments preclude resetting of the step cycle? It may be argued that the timing of the locomotor bursts is determined principally by the speed of the treadmill and, therefore, that it is not possible to observe a resetting of the step cycle. However, subjects can walk at the same speed by various combinations of stride length and stride frequency (e.g., Grillner et al. 1979). There are thus two ''degrees of freedom'' available to the CNS by which to modify a step cycle, despite the requirement of constant speed imposed by the treadmill. Thus one possible interpretation of the lack of resetting of the step cycle is that whatever the function of the motor cortex during human walking, it may not be part of the neural system involved in timing the motor bursts. This interpretation is reinforced by the fact that the silent period following a MEP is largely due to intracortical inhibition (e.g., see Roick et al. 1993). Thus on this basis alone, if the motor cortex were part of the neural system involved in timing aspects of the step cycle, a phase difference of $\sim 0.2-0.3$ should have been observed (i.e., with silent periods lasting up to 200–300 ms for strong stimuli). Our interpretation is also consistent with the conclusion arrived at by Wagener and Colebatch (1997). According to these authors, the resetting of voluntary rhythmical wrist movements following magnetic stimulation of the motor cortex was largely due to the afferent volley following the elicited muscle twitch, but not by an action on what they called the ''motor program.'' Presumably, in our

experiments the elicited muscle twitches were not sufficiently strong to have an effect. Alternatively, the mechanism identified by Wagener and Colebatch may be inoperative during human walking.

The second issue that needs discussion is whether the present results on human subjects differ from those reported for the cat. Orlovsky (1972) and Drew (1991) reported that stimulation of the corticospinal tract or the motor cortex, respectively, can reset the step cycle of cats walking on a treadmill. Drew's interpretation of this result, obtained with a long train of high-frequency stimuli, is that the motor cortex is capable of initiating and controlling corrective actions in situations where a rapid modification of limb trajectory is required, such as when an obstacle suddenly appears in the path of the animal (see also Drew 1993; Widajewicz et al. 1994). We agree with this idea, but our phase-resetting measurements address a different question, namely, whether the motor cortex is involved in timing the human step cycle and not whether the motor cortex is capable of modifying the timing of the step cycle. The method of delivering a single stimulus to the motor cortex during the step cycle is appropriate for answering the former question (e.g., Glass and Mackey 1988; Wagener and Colebatch 1997).

In summary, it was important to attempt to determine whether the motor cortex is involved in some aspect of step cycle timing. We suggest that the human motor cortex is likely to be coupled to the timing network of the locomotor bursts, as shown by Orlovsky and Drew in the cat, but that it is not part of that network.

Epilogue

The results reported in the present study are a beginning toward understanding the nature of cortical control during human walking. Given the observations in this systems-level study, experiments involving single motor unit recordings and more classic approaches, such as conditioning-testing paradigms, will be more clearly interpretable and further our understanding.

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