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Integrated Motor Cortical Control of Task-Related Muscles During Pointing in Humans

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Devanne, Hervé, Leonardo G. Cohen, Nezha Kouchtir-Devanne, and Charles Capaday. Integrated motor cortical control of task-related muscles during pointing in humans. *J Neurophysiol* 87: 3006–3017, 2002; 10.1152/jn.00990.2001. A large body of compelling but indirect evidence suggests that the motor cortex controls the different forelimb segments as a whole rather than individually. The purpose of this study was to obtain physiological evidence in behaving human subjects on the mode of operation of the primary motor cortex during coordinated movements of the forelimb. We approached this problem by studying a pointing movement involving the shoulder, elbow, wrist, and index finger as follows. Focal transcranial magnetic stimulation (TMS) was used to measure the input-output (I/O) curves—a measure of the corticospinal pathway excitability—of proximal (anterior deltoid, AD, and triceps brachii, TB) and distal muscles (extensor carpi radialis, ECR, and first dorsal interosseus, 1DI) during isolated contraction of one of these muscles or during selective co-activation with other muscles involved in pointing. Compared to an isolated contraction of the ECR, the plateau-level of the ECR sigmoid I/O curve increased markedly during co-activation with the AD while pointing. In contrast, the I/O curve of AD was not influenced by activation of the more distal muscles involved in pointing. Moreover, the 1DI I/O curve was not influenced by activation of the more proximal muscles. Three arguments argue for a cortical site of facilitation of ECR motor potentials. First, ECR motor potentials evoked by a near threshold TMS stimulus were facilitated when the AD and ECR were co-activated during pointing but not those in response to a near threshold anodal electrical stimulus. Second, the ECR H reflex was not found to be task dependent, indicating that the recruitment gain of the ECR α-motoneuron pool did not differ between tasks. Finally, in comparison with an isolated ECR contraction, intracortical inhibition tested at the ECR cortical site was decreased during pointing. These results suggest that activation of shoulder, elbow, and wrist muscles involved in pointing appear to involve, at least in part, common motor cortical circuits. In contrast, at least in the pointing task, the motor cortical circuits involved in activation of the 1DI appear to act independently.

INTRODUCTION

The results of classic lesion experiments and single-unit recordings suggest that the motor cortex is involved in the coordination of limb segments during precise movements (reviewed by Kalaska and Drew 1993). However, as most recently emphasized by Scott (2000), it is not clear whether the motor cortex controls each limb segment individually or the limb as a whole. The essence of this controversy stems from disparity between results of single-unit firing activity obtained in experiments involving movement at a single forelimb joints versus those that involved whole-arm reaching movements (see Scott 2000). In contrast, evidence derived from other experimental approaches suggests that the motor cortex functions in an integrative manner as first suggested by Jackson (1931). For example, studies involving the superposition of topographical maps of the motor cortex obtained by microstimulation and morphological connectivity maps obtained by tracer injections in physiologically identified sites have shown that motor cortical zones controlling various forelimb segments and those controlling antagonistic muscles are strongly interconnected by intrinsic horizontal collaterals (Capaday et al. 1998; Huntley and Jones 1991; Keller 1993; Tokuno and Tanji 1993). These intracortical connections may be the anatomical substrate of muscle synergies involved in coordinated multi-joint movements. Additionally, the intrinsic motor cortical connectivity may have its actions reinforced by the extensive intraspinal branching of corticospinal axons (McKiernan et al. 1998; Shinoda et al. 1976; Tantisira et al. 1996). For example, 50% of corticospinal neurons project to both proximal (e.g. shoulder, elbow) and distal muscles (e.g. wrist and hand), some controlling muscles at three different forelimb segments (McKiernan et al. 1998). Further support for the idea of embedded muscle synergies comes from studies by Armstrong and Drew (1985) on the cat motor cortex. They showed that microstimulation, even at threshold, elicits a widespread pattern of muscle activation as we have also observed (Capaday et al. 1998; Schneider et al. 2001). Donoghue et al. (1992) obtained similar results in the squirrel monkey. Our recent experiments have shown that this is not due to the spread of current from the tip of the microelectrode nor the result of impulse conduction along the lengthy intracortical axonal arbors (Schneider et al. 2001).

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Kinematic analysis of human pointing movements has shown that elbow and shoulder motions are tightly coupled (Soechting 1984). The neural basis of this observation remains to be elucidated, but clearly motor cortical circuits may be involved, several observations support this idea. Donoghue et al. (1992) concluded from their mappings of the squirrel monkey motor cortex that "*. . . patterns of organization that include functional combinations of muscles must be considered.*" In Rhesus macaques, it has been suggested that their exists a motor cortical region containing neurons that specify functional synergies of distal and proximal muscles (Park et al. 2001). In humans, Sanes et al. (1995) suggested that the overlap of cortical representation obtained by functional magnetic resonance imaging (fMRI) may mediate motor functions requiring coordinated neural processing for finger and wrist action rather than discrete control implied by somatotopic maps. Schneider et al. (2002) showed that in the cat, distinct motor cortical points might be dynamically linked to form muscle synergies by controlling the activity of GABAergic neurons. Despite this body of compelling but indirect evidence it is, as stated by Scott (2000) "*difficult to assess if and how the motor cortex contributes to the coordination of motor patterns at different joints.*" Here we provide evidence based on neurophysiological measurements in behaving human subjects that the motor cortical control of arm muscles during pointing is of an integrated nature. Our approach involved comparing the input-output (I/O) characteristics of the corticospinal pathway to a given muscle (Devanne et al. 1997) when it was voluntarily activated in isolation versus when it was synergistically activated with muscles acting at other joints while pointing at a target. However, our purpose was not to study pointing per se. Our results relate to movements involving multiple limb segments; pointing was used as a natural task involving the shoulder, arm, and hand. As we will show, the simultaneous control of muscles acting at the shoulder, elbow and wrist involves, at least in part, common motor cortical circuits. A brief account of the work presented here was published as an abstract (Capaday et al. 1999a).

METHODS

The experiments were done on 19 normal human subjects ranging in age between 21 and 42 yr [30 ± 7.4 (SD) yr]. All subjects gave their informed consent after being informed of the nature and purpose of the experiment, which was approved by the local ethics committee.

Experimental rationale

In our study of the input-output properties of the human corticospinal pathway (Devanne et al. 1997), we had shown that the relation between the intensity of magnetic stimuli delivered to the motor cortex and the size of the motor-evoked potentials (MEPs) was sigmoidal. It was also shown that the steepness of the relation, a formal measure of gain, increased with the recruitment level of the motoneuron pool—as measured by the mean value of the rectified electromyographic (EMG) activity—without a change in the plateau level. The increase in the steepness of the relation with motor activity (up to 4–7 times) was much more marked than the decrease of threshold (15–40%). 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). We thus suggested that demonstrating a task-dependent change of corticospinal activity would require a change in one or more of the I/O parameters (threshold slope, plateau) independently of the level of motor activity. In the present investigation, we studied the cortical control of pointing at a visual target, a natural and common gesture. Our reasoning was that if the I/O properties were different when a muscle was voluntarily activated in isolation versus when it was co-active with other muscles during pointing, this would potentially demonstrate a common cortical control. This 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. As it turned out, to establish that the task-dependent change(s) in the I/O relation of a given muscle are of cortical origin, three different and mutually reinforcing methods were used. First, we measured changes in intracortical inhibition (ICI) with paired-pulse magnetic stimuli to the motor cortex (Kujirai et al. 1993). This inhibition has been shown unequivocally to be of intracortical origin (Di Lazarro et al. 1998), and there is pharmacological evidence that it depends on GABAergic neurons (Ziemann et al. 1996). We also compared the size of MEPs elicited by threshold magnetic and anodal electrical stimuli, respectively, for each task. Threshold anodal stimuli activate corticospinal neurons distal to their soma at the first or second node of Ranvier. Consequently, the evoked corticospinal discharge is thought to be relatively uninfluenced by the state of intracortical excitability (Amassian et al. 1987; Rothwell 1997). In contrast, threshold magnetic stimuli activate corticospinal neurons *trans*-synaptically (Rothwell 1997), consequently the evoked corticospinal discharge is thought to have some dependence on the state of intracortical excitability. Third, monosynaptic reflexes of wrist extensors were measured in each task. A task-dependent change in the I/O curve of a given muscle, unaccompanied by a change in monosynaptic reflex amplitude, implies that it is not due to a change of the recruitment gain at the motoneuron pool (Devanne et al. 1997; Kernell and Hultborn 1990).

Experimental protocol and behavioral task

Subjects were comfortably seated in front of two analog meters 20 cm apart. The subjects pointed to a 1-cm circular target with their preferred arm. The target position was adjusted for each subject to be in the parasagittal plane of the arm flexion movement. When the arm was in the pointing position, the target was separated from the tip of the index finger by a few millimeters. The analog meters were placed in front of the subjects medial to the target in such a way they had no difficulty to control both the arm position relative to the target and the EMG levels displayed by the analog meters. A rigid molded Sansplit frame was then adjusted to support the arm, the wrist, and the index finger in the pointing position. This device allowed either complete relaxation of all arm muscles involved in the pointing task or tonic voluntary contraction of isolated muscles without any change of shoulder, elbow, wrist, and index finger joint positions. The brace was built such that by removing one or more sections of the frame, different combinations of voluntary muscle co-activation patterns were obtained. For example, with only the shoulder supported, pointing at the target involved co-activation of the wrist and finger extensors. Conversely, with the finger and wrist supported, pointing involved only shoulder and elbow muscles. In this way, different muscle co-activation patterns involved in pointing could be achieved, including what we will refer to as normal pointing. The maximal EMG activity of each muscle, respectively, was determined while the subjects exerted a maximal isometric contraction. Each analog meter was then calibrated so that a full-scale deflection corresponded to the maximum isometric contraction of the selected muscle. In the text when we refer to activation of a muscle alone, we mean in the absence of activity in the other recorded muscles.

EMG recordings

Pairs of surface Ag-AgCl electrodes were placed over the belly of muscles acting at different joints. The muscles whose activity was recorded were, from distal to proximal, the first dorsal interosseus (1DI), the extensor carpi radialis (ECR), the triceps brachii (TB), and the anterior deltoid (AD), which are co-active during pointing. The electrodes were attached to the skin by O rings of double-sided adhesive film. Inner diameter of AD and TB electrodes was larger (9 mm) than that of ECR and 1DI (1 mm). The electrodes were connected to optically isolated preamplifiers. A large reference electrode connected to the common input of the preamplifiers was placed in the neck region, just above the shoulder on the recording side. The EMG signals were amplified, high-passed at 20 Hz and low-passed at 1 kHz prior to sampling at 4 kHz by an A/D converter. The same signals were also separately amplified, high-pass filtered at 20 Hz, rectified, and low-passed at 100 Hz before sampling at 4 kHz. The mean level of background EMG activity was measured from the rectified signals over a 50-ms time segment just prior to stimulation. Comparison of responses obtained in the different tasks was done for matched levels of background EMG activity.

Percutaneous electrical nerve stimulation

The radial nerve was stimulated through a constant voltage stimulus isolation unit (Grass SIU5) with square pulses of 0.5 ms in duration, using a Ag-AgCl electrode as the cathode placed about 10 cm above the elbow at an optimal point in the spiral groove for eliciting an H reflex in the ECR. The anode, a large metal plate covered in gauze and moistened with saline, was placed on the opposite side of the arm. Because the M wave and H reflex of the ECR overlap, we carefully measured the respective recruitment curves by small increments of the stimulus intensity so as to distinguish between the two potential waveforms. The stimulus intensity used to elicit the ECR H reflex was adjusted to the ECR M-wave threshold. A time-amplitude window discriminator implemented in software ensured that only M waves of specified amplitude were accepted before averaging in real time (Capaday et al. 1995).

Transcranial magnetic stimulation

Magnetic stimuli were applied to the scalp with a focal coil connected to a Cadwell MES-10 electromagnetic stimulator. The coil was coned and double D-shaped, each D-shaped half being 7 cm long $\times$ 8 cm wide. The Cadwell stimulator induces a damped polyphasic current, about 200 μs in duration. Depending on specific experiment, the focal points for activation of the AD, TB, ECR, or 1DI were first localized. The focal point is defined as the lowest threshold site giving a response specifically in the intended muscle at rest. Once the focal point was localized, its locus was marked with a cross hair drawn on the scalp. This served as a visual reference against which the coil was positioned and maintained by the experimenter. The magnetic stimulus intensity was expressed as a percentage of the maximum of the stimulator scale. Stimuli were delivered at random between 3 and 5 s.

Transcranial electrical stimulation

In two subjects, electrical stimuli were applied over the scalp through a radio frequency isolation transformer. Two Ag-AgCl electrodes were used. The cathode was placed at the vertex, while the anode was placed over the optimal scalp position for magnetic stimulation. Square pulses of 200 μs duration were delivered at random between 3 and 5 s. The stimulus intensity that evoked a threshold response in the voluntarily activated ECR was first determined and defined as the active motor threshold (AMT). The stimulus strength was then adjusted so as to produce MEPs of comparable size to those produced by threshold magnetic stimuli under corresponding conditions.

Measurement of I/O curves

Transcranial magnetic stimulation (TMS) of increasing intensity were delivered to the optimal scalp position for stimulation of a selected muscle in each of the tasks. The TMS intensity was increased in steps of 2–4%, until the plateau level of the characteristic sigmoidal relation was reached (Devanne et al. 1997). The I/O curve parameters have been shown to be independent of whether the stimulus intensity is delivered with increasing, decreasing or in random order (Capaday et al. 1999b; Devanne et al. 1997). The effect of order of presentation of stimulus intensities was tested in one subject and the results were consistent with those of our previous studies.

In all experiments, I/O curves of a target muscle were measured in four tasks. The task order was randomized for each subject. The EMG activities of the various muscles were monitored on a multi-channel oscilloscope and via audio monitors. In the first condition, the subject was asked to maintain all upper limb muscles quiescent while all limb segments were fully supported by the bracing system and the limb oriented to point at the target (passive pointing). In the second condition, the subject was asked to actively point at the target (i.e., no limb segment was braced), we will refer to this task as normal pointing. In the third condition, the subject was asked to produce an isolated contraction of a selected muscle at the same level of activity as occurred during normal pointing (isolated contraction). In the fourth condition, the selected muscle was forced to be co-active with muscles at a different joint (e.g., wrist and shoulder co-active).

TES vs. TMS paradigm

Transcranial electrical stimulation (TES) was applied in two conditions. First, stimuli at 1.1 $\times$ AMT were delivered while ECR was activated alone at the same level of motor activity as during the pointing task. Then stimuli at the same intensity were applied while the subjects voluntarily co-activated the AD and ECR muscles while pointing at the target. MEP amplitudes were measured in each condition and compared to MEPs elicited by TMS in the same two tasks.

Paired-pulse magnetic stimulation

Two Magstim 200 stimulators connected by a BiStim module allowed us to deliver two magnetic pulses through the same figure-of-eight coil used for the I/O curve measurements. The ECR's AMT was determined while the subjects contracted the ECR at the same level of activity as during normal pointing. Then paired stimuli were delivered with a conditioning stimulus of 0.8 AMT, and a test stimulus of either 1.1 or 1.2 AMT depending on the subjects. The conditioning-testing intervals ranged between 2 and 15 ms. We then focused on the two best intervals, i.e., those at which greatest ICI and ICF were obtained, respectively. The measurement of interest was to compare the amount of ICI and ICF when the ECR was activated alone versus when it was co-activated with AD. As will be reported, during co-activation of the ECR and AD the ECR MEPs are larger. However, by appropriately reducing the stimulus intensity during co-activation, the measurements were done for similar ECR test MEP amplitudes (Chen et al. 1998).

Curve fitting and statistical analysis

For TMS experiments, four to eight stimuli were evoked at a given intensity in each series of experiments and averaged over a 250-ms time window including 50 ms prior to the stimulus. The peak-to-peak value of the MEP was measured from non-rectified EMG signals, and the area under the MEP was determined from rectified channels. For each muscle, the mean contraction level was calculated over the

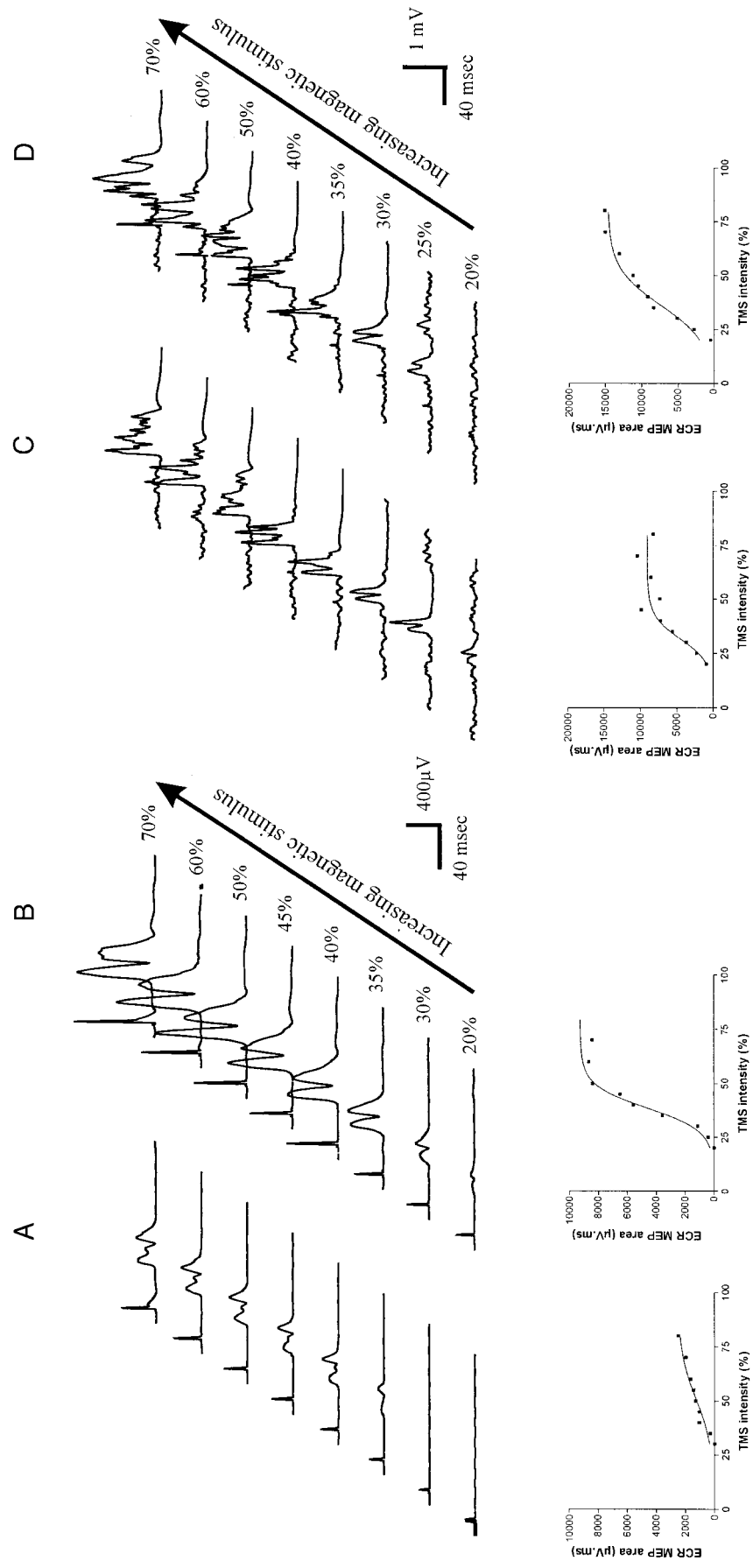

FIG. 1. Recordings of extensor carpi radialis (ECR) motor-evoked potentials (MEPs) evoked by transcordial magnetic stimulation (TMS) at increasing stimulus intensities. *A* and *B*: the ECR was at rest. The anterior deltoid (AD) was also at rest in *A* but activated while pointing in *B*. *C* and *D*: the ECR was voluntarily activated alone (*C*) or co-activated with the AD (*D*) while pointing. The background level of electromyo-graphic (EMG) activity (mean ± SE) was 110 ± 3.9 μV in *C* and 99.6 ± 4.0 μV in *D*, the difference is not significant. Under each panel of MEP recordings, the corresponding input/output (I/O) curve relating the stimulus intensity to the ECR MEP integral is shown. Note the marked effect of AD activation on the I/O curves of the resting or active ECR.

50-ms period prior to the stimulus; this value was subtracted from each point of the corresponding rectified channel before determining the MEP area. The Boltzmann sigmoidal function was used to fit the data by the Levenberg-Marquard nonlinear least-mean-square algorithm (Press et al. 1986). This equation accounts for at least 80% of the total variance ($R^2 > 0.8$) and is a significantly better fit to the data than a straight line (Devanne et al. 1997). The Boltzmann equation relating the integral or the peak-to-peak amplitude of the response (MEP) and the stimulus intensity (S) is given by the following equation

$$\mathrm{MEP}(S) = \frac{\mathrm{MEP}_{\max}}{1 + e^{\left(\frac{S_{50} - S}{k}\right)}}$$

The three parameters of this function are, respectively: the plateau level ($\mathrm{MEP}_{\max}$), the stimulus intensity (S_{50}) required to obtain a response 50% of the plateau value (i.e. the maximum), and the slope parameter k. The curve is steepest at S_{50} and the slope at this point is $\mathrm{MEP}_{\max}/4k$.

To determine task-dependent statistical differences between the I/O curves, three different methods were used as we have done in a previous study (see details in Capaday et al. 1999b and references therein). 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 ($\mathrm{MEP}_{\max}$, S_{50}, 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 to fitting a single curve to all the data sets. This is formally equivalent to a multiple analysis of variance. The third method is a between-subjects (i.e., across all repetitions of the experiment) comparison for each estimated parameter using a *t*-test for correlated samples. The results of all three methods were consistent with each other, as we have observed in a previous study (Capaday et al. 1999b). In the experiments involving TES or those involving H reflexes, we compared the peak-to-peak amplitude, or integral values of the MEPs, obtained in two conditions (2 muscles co-activated vs an isolated contraction) using a paired *t*-test.

RESULTS

We first describe the influence of shoulder muscle activation on the I/O curves of elbow and wrist muscles during pointing. It will be shown that the I/O curves of the ECR and TB while pointing are strongly dependent on activity of the AD. In contrast, the I/O curve of the AD was not influenced by activation of elbow and wrist muscles. We then describe the influence of proximal muscle activation on the finger muscle I/O curve. It will be shown that during pointing the I/O curve of the 1DI is independent of activity in more proximal muscles. The remaining sections deal with determining the site of origin of the task-dependent effects and the general nature of the underlying neural mechanisms.

Influence of shoulder muscle activation on the I/O curves of elbow and wrist muscles

In this task, the index finger was braced and no EMG activity was present in the 1DI. When pointing required activity in shoulder muscles (i.e., the arm was not supported), striking changes of wrist and elbow muscle I/O curves were observed. Figure 1 illustrates the change in ECR MEPs associated with voluntary contraction of the AD. AD activation increased the ECR MEPs whether the ECR was at rest (Fig. 1, *A* and *B*), or active (Fig. 1, *C* and *D*). The relation between MEP amplitude and stimulus intensity (i.e. the I/O curves) are shown beneath each panel of Fig. 1. The most salient task-dependent change of the sigmoid ECR I/O curves is the increased plateau. Another example, taken from a different subject, is shown Fig. 2, *A* and *B*. The graphs show the effects of AD activation on the I/O curves of the ECR, either at rest (Fig. 2*A*) or when the ECR was active (Fig. 2*B*). Once again, the increase of the plateau level associated with activation of the AD is the most striking effect on the ECR I/O curves.

The quantitative effect of AD activation on the ECR I/O curve parameters was determined by statistical analysis. In all subjects, activation of the AD increased the plateau level of the resting ECR I/O curve (Fig. 3, top left). The slope and S_{50} of the curve were not significantly different, except in one subject in which the S_{50} value was significantly decreased when the AD was voluntarily activated (Fig. 3, *bottom left*). Compared to activation of the ECR alone, co-activation of ECR and AD also led to an increase of the plateau-level in all except one subject (Fig. 3, *top right*). This increase was significant in 5/8 subjects, not significant in 2, whereas in subject AP, the ECR plateau level was significantly reduced during co-activation of the AD and ECR. In the two subjects in whom the I/O curves of the TB were measured, activation of the AD led to a significant increase of the plateau level of the I/O curve of the resting or active TB.

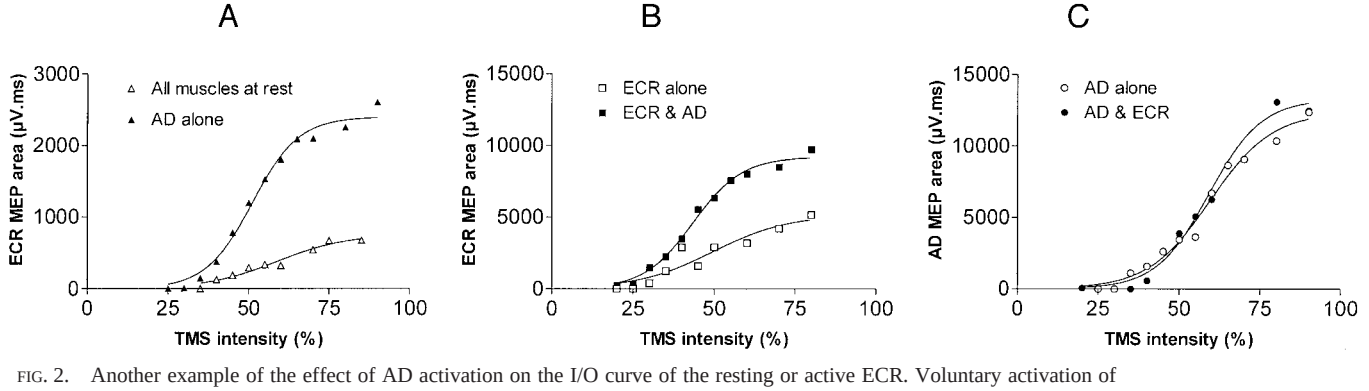

FIG. 2. Another example of the effect of AD activation on the I/O curve of the resting or active ECR. Voluntary activation of the AD increased the plateau value of the resting (*A*) or active ECR I/O curve (*B*). In contrast, none of the parameters of AD I/O curve were affected by co-activation with the ECR (*C*). The mean background level of EMG activity in the AD was 144.6 ± 6.0 μV (AD alone) vs. 151.2 ± 6.5 μV (AD and ECR); the difference is not statistically significant. Note that because the AD could be activated at rest, only 3 conditions can be shown.

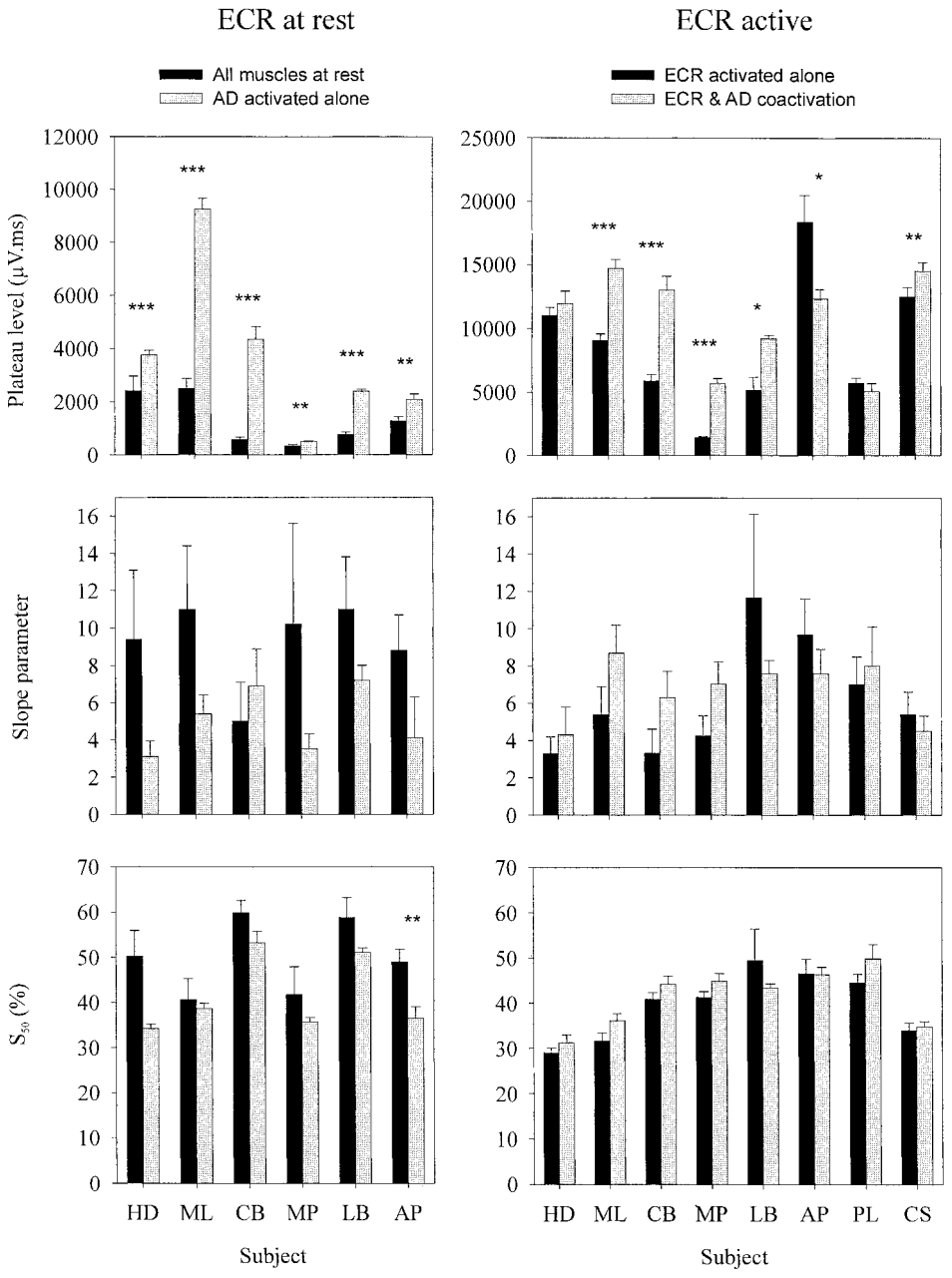

FIG. 3. Statistical summary of the influence of AD activity on the ECR I/O curve parameters when the ECR was at rest (*left*) and when it was active (*right*). Activation of the AD significantly increased the plateau level of the I/O curves but had no significant effect on the other I/O curve parameters. Each bar represents the mean ± SE value of the particular parameter for each subject. The number of stars near an error bar indicates the level of significance (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

In summary, the results of this first set of experiments showed that in the pointing task, when the AD was voluntarily activated, the I/O curves of the TB (elbow) and ECR (wrist) muscles reached a higher plateau level compared to when the AD was quiescent. The difference between the I/O curve parameters cannot be due to the differences in the level of ECR motor activity because the measurements were made at matched levels of EMG activity. The values of the mean background EMG activities in each task are given in the legends of Figs. 1 and 2.

Influence of elbow and wrist muscle activation on shoulder muscle I/O curves

During the initial exploration for localizing the focal sites for the 1DI, ECR, and AD, MEPs restricted to the AD muscle were never observed when the upper limb muscles were at rest. This was also true during voluntary contraction of the AD on its own. In other words, a so-called pure AD focal site was never observed. However, when the ECR optimal site was stimulated, a MEP was always elicited in the AD when this muscle was minimally activated. We thus studied AD responses evoked by magnetic stimulation applied at the ECR site. In contrast to that reported in the preceding section, the I/O curve of the AD was not influenced by activation of elbow and wrist muscles. As can be seen in the example shown in Fig. 2*C*, there was generally no statistical difference between the AD I/O curves measured with and without ECR voluntary activity. In 4/6 subjects there was no change of the plateau-level of the sigmoidal function (Fig. 4). In the two other subjects, this parameter was increased during ECR activity in one and decreased in the other. Finally, the slope and the S_{50} parameter were not significantly changed in 5/6 subjects (Fig. 4).

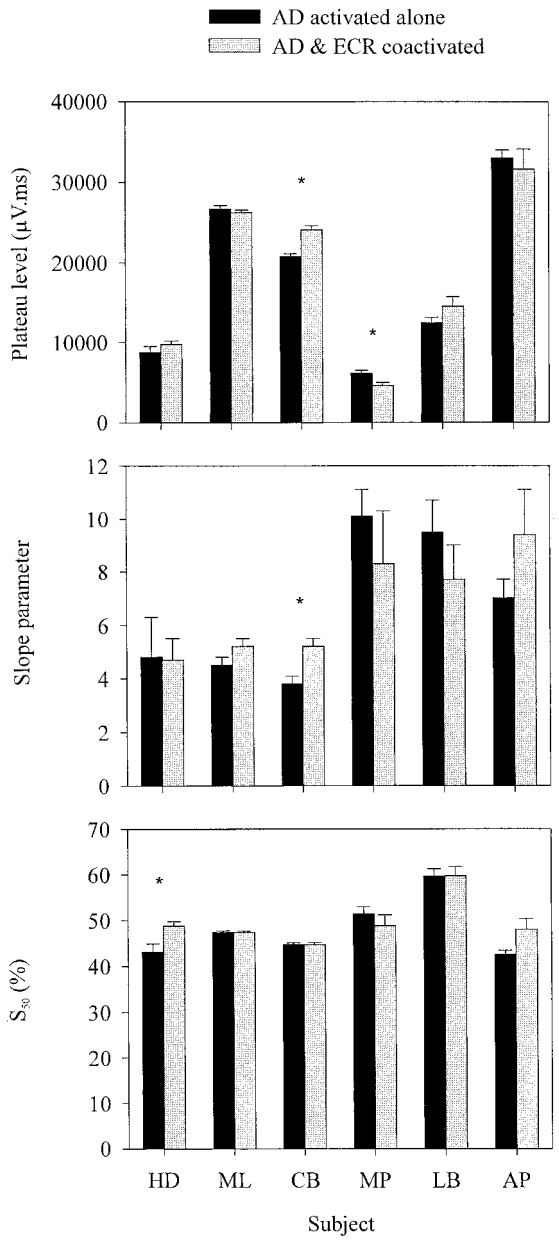

FIG. 4. Statistical summary of the influence of ECR activity on the AD I/O curve parameters. Activation of the ECR did not significantly change the AD I/O curve parameters. Each bar represents the mean ± SE. The format of this figure is similar to that of Fig. 3.

Influence of proximal muscle activation on finger muscle I/O curves

In this task, the finger was used actively while pointing at the target. The magnetic stimuli were applied at the optimal 1DI site, and we measured the influence of ECR and AD voluntary activation on the 1DI MEPs. Some subjects had difficulty activating the 1DI without some activity in the ECR. Only subjects that were able to maintain tonic EMG activity in the 1DI without activating the ECR were studied. We first considered the case where the arm was supported, thus pointing involved activity at the wrist and finger only. All measurements were made at matched levels of 1DI activity. Compared with the I/O curve of the 1DI activated alone, co-activation of ECR and 1DI did not modify the plateau level of the 1DI I/O curve in 4/6 subjects (Fig. 5, *left*). In one of the two other subjects, the plateau reached a greater level ($P < 0.001$) when 1DI was activated alone compared to co-activation with the ECR (40.07 ± 1.27 vs. 32.8 ± 1.44 mV/ms). Conversely, in the other subject the plateau value was significantly increased ($P = 0.025$) when the two muscles were co-activated (8.45 ± 0.35 vs. 10.13 ± 0.67 mV/ms). It is noteworthy that the changes in the plateau values in these two subjects, although statistically significant, were very small compared to the changes of the ECR plateau value associated with activation of the AD. None of the other parameters of the 1DI I/O curve showed any systematic and significant task-dependent changes (Fig. 5). Similarly, the ECR I/O curve was not modified during co-activation with the 1DI.

By releasing the arm support, pointing at the target required shoulder and elbow activity (i.e. normal pointing). Activation of the proximal muscles did not change the plateau level of the 1DI I/O curve in any of the three subjects tested. None of the other parameters of the 1DI I/O curve showed any systematic and significant changes when the AD was active (Fig. 5, *right*).

Influence of shoulder muscle activation on ECR MEPs evoked by TES vs. TMS

In the two subjects studied, near threshold (1.1 × AMT) anodal TES did not lead to any change of the ECR MEP amplitude when the AD and the ECR were co-activated, compared to the condition in which the ECR was activated alone (Fig. 6). In marked contrast, at the same levels of ECR and AD motor activity, near threshold (1.1 × AMT) TMS significantly increased the ECR MEP amplitude when the AD became active (Fig. 6).

Influence of shoulder muscle activation on wrist muscle H reflexes

In four subjects, the ECR H reflex was elicited during an isolated contraction of the ECR and when the ECR and AD were co-activated during pointing, at matched levels of ECR EMG activity in the two tasks. An example of the data recorded in one subject is shown in Fig. 7*A*. It can be seen that the H-reflex amplitude is of near equal amplitude in the two tasks, whereas the ECR MEP elicited by near threshold TMS is markedly enhanced during co-activation with the AD. In three among four subjects, the H-reflex amplitude was not significantly different between the two tasks (Fig. 7*B*). In the fourth subject, the ECR H-reflex amplitude was significantly lower when the AD and ECR were activated together (Fig. 7*B*, *subject GR*). In contrast, in all subjects, the ECR MEP amplitude was significantly greater when the AD and ECR were co-activated during pointing, compared to an isolated contraction of the ECR.

ICI/ICF experiments

In four subjects, we compared the amount of intracortical inhibition (ICI) and facilitation (ICF) of ECR MEPs during an isolated contraction of the ECR versus when the ECR was co-activated with the AD during pointing. At short ISIs (2–4 ms depending on the subject), co-activation of AD and ECR was associated with a significant reduction of inhibition ($t = 3.325$, $P = 0.0159$) of the test ECR MEPs in all four subjects,

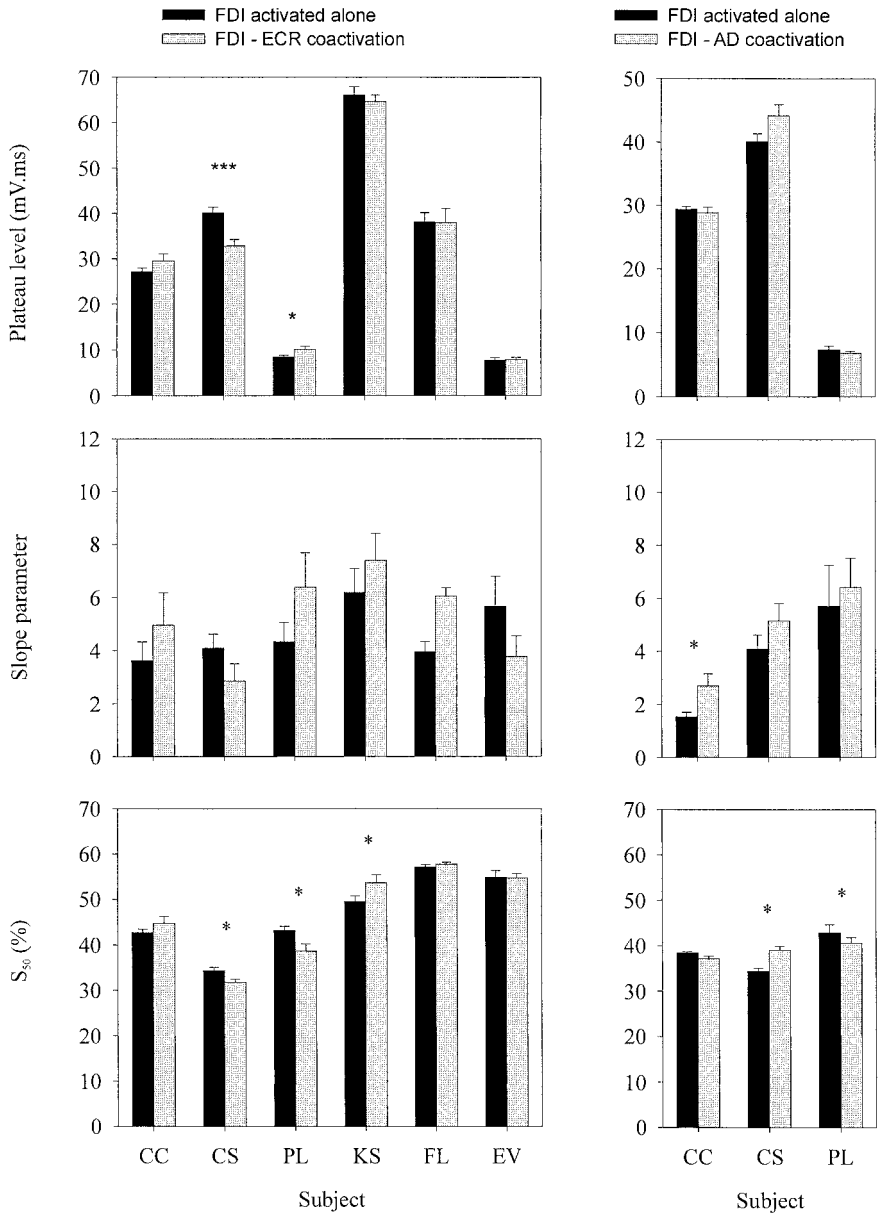

FIG. 5. Statistical summary of the effects of ECR activation (*left*) or AD activation (*right*) on the 1DI I/O curve parameters. In each subject, statistical comparison was made for each parameter of the I/O curve between 2 conditions (isolated 1DI contraction vs. co-activation with the ECR or AD). Each bar represents the mean ± SE. The format of this figure is the same as that of Fig. 3.

an example is shown in Fig. 8. On average, the test ECR MEP was reduced by 67.4 ± 10.9% of control during activation of the ECR alone and by 31.8 ± 18.4% of control during co-activation of the ECR and AD. In other words, ICI was significantly reduced during co-activation of the ECR and AD while pointing in comparison to an isolated contraction of the ECR at matched levels of ECR EMG activity. Task-dependent changes in ICF were not observed.

DISCUSSION

We tested the hypothesis of common versus separate motor cortical control of task-related muscles during pointing. In the event, two main observations were made. First, the plateau level of the ECR and TB I/O curves increased during pointing compared to an isolated contraction of each muscle, respectively. This was due to the added activation of the AD during pointing. In contrast the AD I/O curve was uninfluenced by activation of the more distal muscles involved in pointing. Second, the I/O curve of an intrinsic hand muscle, the 1DI, was uninfluenced by activation of the more proximal muscles involved in pointing. Because the relevant measurements were made at matched levels of EMG activity, the difference between the I/O curve parameters cannot be due to differences in the recruitment level of the α-motoneuron pool. The lack of task-dependent changes of the ECR H reflex eliminates the possibility that the enhanced ECR MEPs were due to task-dependent differences of the recruitment gain of the ECR α-motoneuron pool (Devanne et al. 1997; Kernell and Hultborn 1990). To establish that the site of change was at the motor cortical level, we investigated responses to near threshold anodal versus magnetic stimulation of the motor cortex and measured task-dependent changes in ICI and ICF. It was shown that, during co-activation of the ECR and the AD while pointing, the ECR MEPs elicited by near threshold anodal stimuli were not facilitated compared to activity of the ECR alone. In marked contrast, ECR MEPs elicited by near thresh-

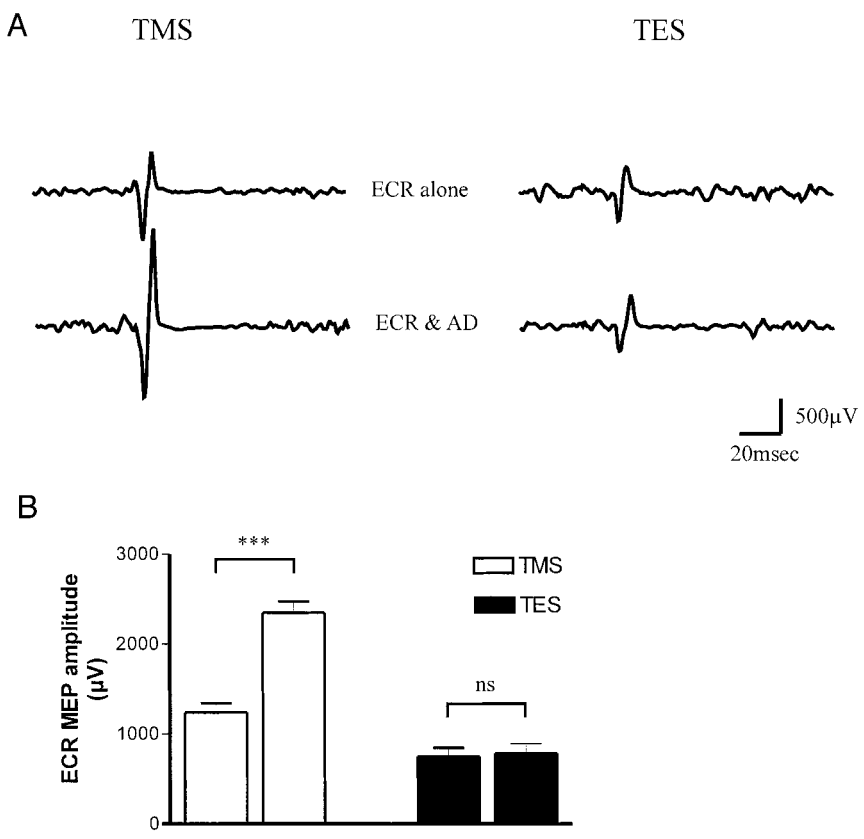

FIG. 6. MEPs evoked by near threshold TMS or by near threshold transcordial electrical stimulation (TES). Each trace in *A* is the average of 8 individual responses. Note how the ECR MEPs elicited by near threshold TMS (1.1 × AMT) are enhanced when the ECR and AD are co-active (*A, left*). In contrast, ECR MEPs elicited by near threshold TES (1.1 × AMT) are not enhanced when the ECR and AD are co-active (*A, right*). The bar graph in part summarizes the effect of the voluntary recruitment of AD on ECR MEP amplitude following TMS (□) and TES (■). Using TMS, the ECR MEP amplitude was significantly increased ($P < 0.001$), whereas no change occurred with TES. During TMS trials, the background EMG activity of the ECR was 45.9 ± 14 μV when activated alone and 37.9 ± 12 μV when co-active with the AD. During TES, the background EMG activity of the ECR was 39.6 ± 18 μV when activated alone and 50.1 ± 31 μV when co-active with the AD. The background EMG activity of the ECR was not significantly different in any task.

old magnetic stimuli were strongly facilitated, evidence that the effects on the I/O curves are of intracortical origin (Rothwell 1997). Added to this, was the observation that ICI, measured on test ECR MEPs, was reduced when the ECR and AD were co-active during pointing in comparison to an isolated contraction of the ECR. This further reinforces the conclusion that the changes in the ECR I/O curves reflect changes at the motor cortical level because ICI has been shown unequivocally to be of intracortical origin (Di Lazzaro et al. 1998).

In the discussion that follows we will consider the functional significance of our observations, how they relate to the results of other studies, and the potential neural mechanisms underlying the observed I/O curve changes.

Functional significance

In our experiments, we observed that voluntary co-activation of AD and ECR muscles led to an increased plateau of the ECR I/O curve, whereas the AD I/O curve was unaffected by voluntary contraction of the ECR, TB, or 1DI. Isolated activation of the AD was also accompanied by a marked modification of the resting ECR and TB I/O curves. These observations may be important clues on the motor cortical mechanisms involved in the control of distal versus proximal muscles. We suggest that the motor cortical circuits controlling shoulder muscles are spatially intertwined and functionally dependent on those that control more distal muscles, such as at the wrist and elbow. This makes sense if one considers that movements of the proximal joints, such as the shoulder, have as their main purpose to move and orient the more distal joints of the elbow and wrist. It may therefore be advantageous for the neural circuits controlling shoulder muscles to be functionally linked and spatially intertwined with those controlling the elbow and wrist. In their synthetic review of a large body of experimental data on the motor cortex, Sanes and Schieber (2001) reached a similar conclusion. Indeed, the experimental results of Amassian et al. (1995) showed that the motor cortical representations of human shoulder muscles are intertwined with those of more distal muscles and distributed over a wide area. What the present physiological measurements demonstrate is that this static feature of the "motor cortex map" manifests itself dynamically during voluntary motor activity. Our neuro-behavioral observations during human pointing are also in keeping with the microstimulation results of Donoghue et al. (1992). These authors reported that in the squirrel monkey the number of motor cortical sites from which shoulder muscles were activated was nearly equal to those from which wrist muscles were activated. They also emphasized the overlap of shoulder and wrist points as was also observed in the cat motor cortex (Schneider et al. 2001). An even more striking connection exists between the present observations and those of Park et al. (2001). They showed that in the forelimb area of the motor cortex of rhesus macaques there exists a central core in which distal muscles are represented (finger, hand, wrist), surrounded by a "horseshoe"-shaped zone in which proximal muscles (shoulder, elbow) are represented. In between these two zones, they found a relatively large zone in which distal and proximal muscles are represented. They suggested that this zone contains neurons that specify functional synergies of distal and proximal muscles. Our observation that the ECR MEPs are greatly enhanced when co-active with the AD may well be a functional manifestation of this organization.

It has been suggested that task precision leads to increased

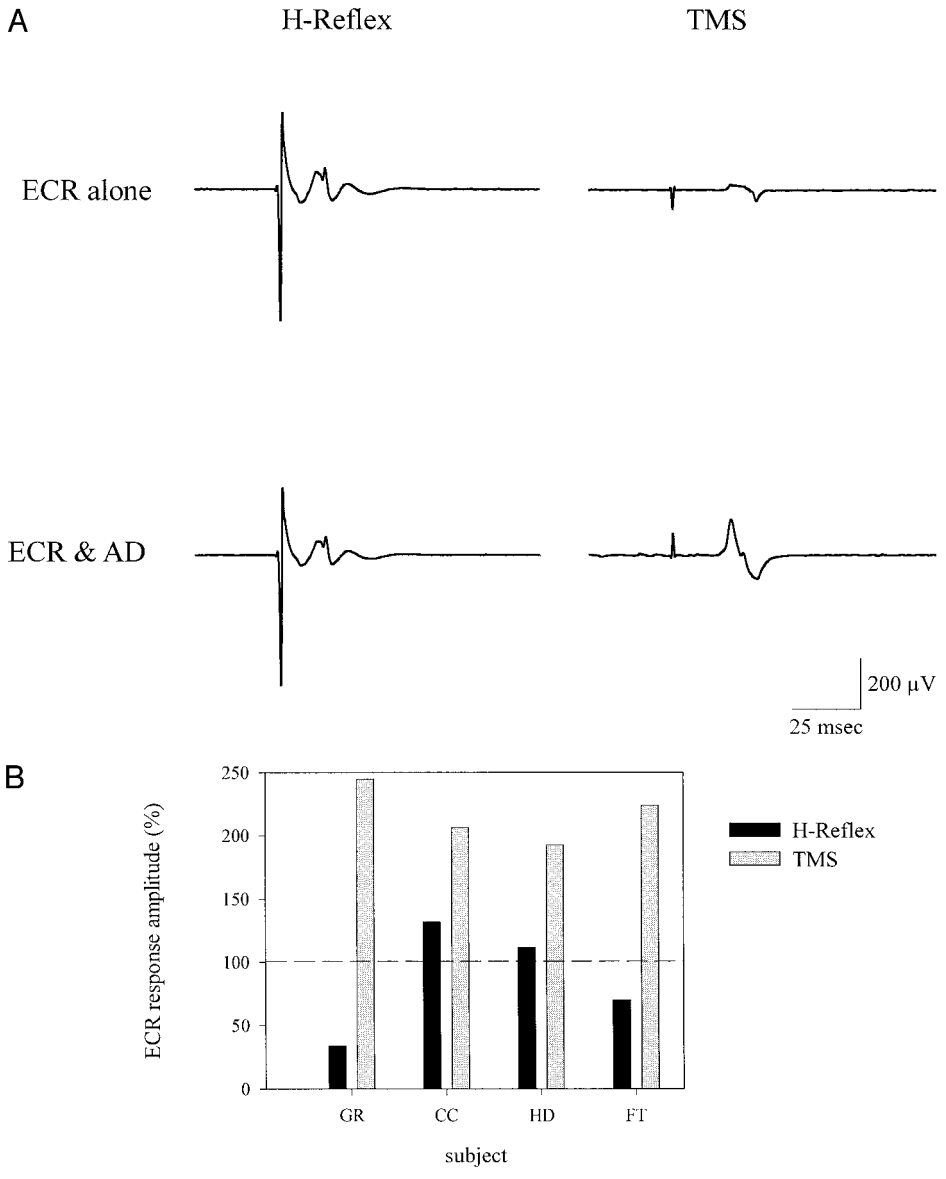

FIG. 7. Example taken form 1 subject of H-reflex responses and MEPs evoked in the ECR when it was activated alone or co-activated with the ECR (*A*). In wrist muscles, the H reflex partly overlaps with the M wave, in the examples shown the H reflex begins a little after the sharp notch in the recordings. In the *2 top traces*, the ECR was activated alone; in the *2 bottom traces*, it was co-active with the AD. Each trace in *A* is the average of 8 consecutive responses. In contrast to the enhanced ECR MEPs when the ECR and AD were co-active, the ECR H reflex was not increased in the same condition. The bar graph in *B* summarizes the data obtained in the 4 subjects studied. The ordinate value is the ratio of the ECR response amplitude between the 2 conditions, ECR and AD vs. ECR alone, expressed as a percentage. In all cases the ECR MEP was enhanced when the ECR and AD were co-active. The background ECR EMG activity prior to stimulation was not significantly different between tasks.

MEPs as a result of greater excitability of the motor cortex (e.g., Datta et al. 1988; Schieppatti et al. 1996). The protocol of Schieppatti et al. (1996) involved the whole arm and hand in tasks that were primarily either postural, power producing, or requiring precise control of force. They observed that MEPs in a given muscle (e.g., AD, 1DI) were greater when it was involved in the precision control of force and suggested that this modulation probably reflected changes in excitability at the cortical level. However, in their study the influence of muscles active at other joints was not systematically taken into account. We suggest that, in addition to the potential influence of task precision, simultaneous cortical control of distal and proximal muscles (e.g., ECR and AD) is reflected by enhanced MEPs.

In our study, the I/O curve parameters of the 1DI showed no dependence on activation of more proximal muscles. A possible explanation for this result may be that the control of finger position in our pointing task was not precise enough, the control of end-point position being mainly due to the more proximal muscles. But the result could also reflect an independent cortical control of finger muscles during the pointing task. Perusal of motor cortex maps derived by microstimulation shows a large number of independent finger zones, while others are intermingled with wrist, elbow, and even shoulder zones (e.g., Donoghue et al. 1992; Gould et al. 1986; Park et al. 2001). Single-unit recordings in behaving monkeys (Schieber and Hibbard 1993) and functional MRI imaging during motor-task performance in humans (Sanes et al. 1995) also show extensive overlap of wrist- and finger-related activity. However, such studies do not demonstrate, per se, mutual interactions and functional coupling within a cortical area as our approach does. Thus it may be suggested that in some tasks, such as pointing, finger movements may be controlled independently of more proximal forelimb muscles but that common motor cortical control may occur in other tasks, such as object manipulation. This point merits further investigation.

Neural mechanisms

An isolated voluntary contraction is accompanied by a decrease of ICI (Kujirai et al. 1993; Ridding et al. 1995). More

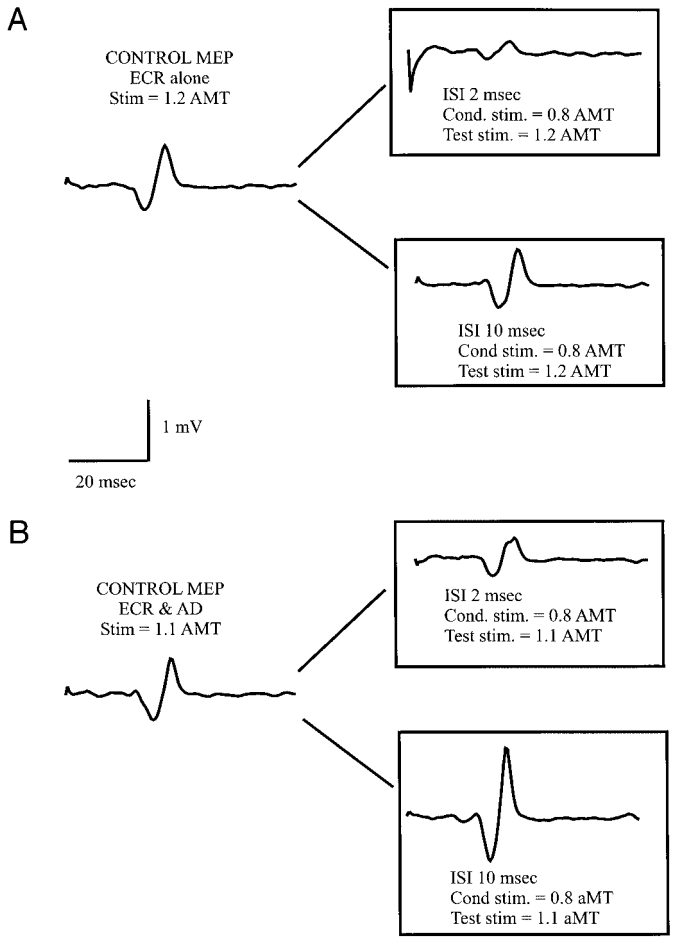

FIG. 8. Example showing that co-activation of AD and ECR led to a decrease of intracortical inhibition (ICI) compared to when the ECR was activated alone. Compare the size of the MEP at an ISI of 2 ms in *A* vs the 1 in *B*. The background level of ECR EMG activity for the 3 conditions illustrated in *A* (rest, ISI 2 ms, ISI 10 ms) was, 49 ± 15, 53 ± 18, and 44 ± 15 μV, respectively. In *B*, the values were 43 ± 13, 41 ± 11, and 57 ± 18 μV, respectively. Note that in this subject, at an ISI interval of 10 ms (ICF), facilitation was observed, but this was the only case (*B*). The slightly higher value of the background ECR EMG, although not significantly different from the others, may account for this.

recently, Liepert et al. (1998) reported that ICI is also task dependent. These authors concluded that ICI is a highly specific phenomenon differentially modulated by the requirements of the motor task. In the present experiments, we observed a decrease of ICI in the ECR cortical site when the AD was co-activated with the ECR. This observation shows that co-activation of these muscles during pointing was accompanied by a further reduction of ICI. This suggests that the cortical circuits underlying ICI may be specifically engaged during synergistic activation of muscles.

In contrast to the decrease of ICI during pointing, ICF did not change. This was also observed in the study of Liepert et al. (1998) and adds to the evidence that ICI and ICF are mediated by different neural mechanisms. Thus the increased plateau value of the ECR I/O curve associated with its co-activation with the AD appears linked with a decrease of ICI rather than an increase of intracortical excitability as measured by ICF. On this basis, it may be suggested that the increased plateau of the ECR I/O curves results from activation of a greater number of corticospinal neurons made more excitable as a result of reduced inhibition.

Epilogue

The idea of common motor cortical control of the musculature dates back to Jackson (1931) and was based on his observations of the pattern of movements evoked during motor cortical seizures. Here we have provided physiological evidence in normal human subjects that the simultaneous control of wrist, elbow, and shoulder muscles during pointing involves common motor circuits—i.e., they are controlled in an integrated manner. However, as stated in the INTRODUCTION, we do not claim that this is specific to pointing, per se. Our results relate to movements involving multiple limb segments, pointing was used as a natural multi-joint task. The approach we have taken here can be fruitfully extended to further our understanding of the nature of motor cortical control during other types of voluntary motor tasks.

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REFERENCES

AMASSIAN VE, CRACCO RQ, MACCABEE PJ, CRACCO JB, AND HENRY K. Some positive effects of transcranial magnetic stimulation. In: *Advances in Neurology, Negative Motor Phenomena*, edited by Fahn S, Hallett M, Lüders HO, and Marsden CD. Philadelphia, PA: Lippincott-Raven, 1995, vol. 67, p. 79–106.

AMASSIAN VE, STEWART M, QUIRK GH, AND ROSENTHAL JL. Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery* 20: 74–93, 1987.

ARMSTRONG DM AND DREW T. Electromyographic responses evoked in muscles of the forelimb by intracortical microstimulation in the cat. *J Physiol (Lond)* 367: 309–326, 1985.

CAPADAY C. Neurophysiological methods for studies of the motor system in freely moving human subjects. *J Neurosci Methods* 74: 201–218, 1997.

CAPADAY C, DEVANNE H, BERTRAND L, AND LAVOIE BA. Intracortical connections between motor cortical zones controlling antagonistic muscles in the cat: a combined anatomical and physiological study. *Exp Brain Res* 120: 223–232, 1998.

CAPADAY C, DEVANNE H, KOUCHTIR N, MERCIER I, AND COHEN LG. Lateral interactions within the motor cortex during pointing. *Soc Neurosci Abstr* 25: 1408, 1999a.

CAPADAY C, LAVOIE BA, BARBEAU H, SCHNEIDER C, AND BONNARD M. Studies of the corticospinal control of human walking. I. Responses to focal transcranial magnetic stimulation of the motor cortex. *J Neurophysiol* 81: 129–139, 1999b.

CAPADAY C, LAVOIE BA, AND COMEAU F. Differential effects of a flexor nerve input on the human soleus H reflex during standing versus walking. *Can J Physiol Pharmacol* 73: 436–449, 1995.

CAPADAY C AND STEIN RB. A method for stimulating the reflex output of a motoneuron pool. *J Neurosci Methods* 21: 91–104, 1987.

CHEN R, TAM A, BUTEFISCH C, CORWELL B, ZIEMANN U, ROTHWELL JC, AND COHEN LG. Intracortical inhibition and facilitation in different representations of the human motor cortex. *J Neurophysiol* 80: 2870–2881, 1998.

DATTA AK, HARRISON LM, AND STEPHENS JA. Task-dependent changes in the size of response to magnetic brain stimulation in human first dorsal interosseus muscle. *J Physiol (Lond)* 418: 13–23, 1988.

DEVANNE H, LAVOIE BA, AND CAPADAY C. Input-output properties and gain changes in the human corticospinal pathway. *Exp Brain Res* 114: 329–338, 1997.

DI LAZZARO V, RESTUCCIA D, OLIVIERO A, PROFICE P, FERRARA L, INSOLA A, MAZZONE P, TONALI P, AND ROTHWELL JC. Magnetic transcranial stimulation at intensities below active motor threshold activates inhibitory circuits. *Exp Brain Res* 119: 265–268, 1998.

DONOGHUE JP, LEIBOVIC S, AND SANES JN. Organization of the forelimb area in squirrel monkey motor cortex: representation of digit, wrist, and elbow muscles. *Exp Brain Res* 89: 1–19, 1992.

GOULD HJ, CUSICK CG, PONS TP, AND KAAS JH. The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *J Comp Neurol* 247: 297–325, 1986.

HUNTLEY GW AND JONES EG. Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. *J Neurophysiol* 66: 390–413, 1991.

JACKSON JH. *Selected Writings of John Hughlings Jackson.* London: Hodder and Stroughton, 1931.

KALASKA JF AND DREW T. Motor cortex and visuomotor behavior. *Exer Sports Sci Rev* 21: 397–436, 1993.

KELLER RB. Outcomes research in orthopedics. *J Am Acad Orthop Surg* 1: 122–129, 1993.

KERNELL D AND HULTBORN H. Synaptic effects on recruitment gain: a mechanism of importance for the input-output relations of motoneuron pools? *Brain Res* 507: 176–179, 1990.

KUJIRAI T, CARAMIA MD, ROTHWELL JC, DAY BL, THOMPSON PD, FERBERT A, WROE S, ASSELMAN P, AND MARSDEN CD. Corticocortical inhibition in human motor cortex. *J Physiol (Lond)* 471: 501–519, 1993.

LIEPERT J, CLASSEN J, COHEN LG, AND HALLETT M. Task-dependent changes of intracortical inhibition. *Exp Brain Res* 118: 421–426, 1998.

MCKIERNAN BJ, MARCARIO JK, KARRER JH, AND CHENEY PD. Corticomotoneuronal posspike effects in shoulder, elbow, wrist, digit, and intrinsic hand muscles during a reach and prehension task. *J Neuropysiol* 367: 1961–1980, 1998.

PARK MC, BELHAJ-SAÏF A, GORDON M, AND CHENEY PD. Consistent features in the forelimb representation of primary motor cortex in Rhesus macaques. *J Neurosci* 21: 2784–2792, 2001.

PRESS WH, FLANNERY BP, TEUKOLSKY SA, AND VETTERLING WT. *Numerical Recipes.* Cambridge, UK: Cambridge University Press, 1986.

RIDDING MC, TAYLOR JL, AND ROTHWELL JC. The effect of voluntary contraction on cortico-cortical inhibition in human motor cortex. *J Physiol (Lond)* 487: 541–548, 1995.

ROTHWELL JC. Techniques and mechanisms of action of transcranial stimulation of the human motor cortex. *J Neurosci Methods* 74: 113–122, 1997.

SANES JN, DONOGHUE JP, THANGARAJ V, EDELMAN RR, AND WARACH S. Shared neural substrates controlling hand movements in human motor cortex. *Science* 268: 1775–1777, 1995.

SANES JN AND SCHIEBER MH. Orderly somatotopy in primary motor cortex: does it exist? *Neuroimage* 13: 968–974, 2001.

SCHIEBER MH AND HIBBARD LS. How somatotopic is the motor cortex hand area. *Science* 261: 489–492, 1993.

SCHIEPPATI M, TROMPETTO C, AND ABBRUZZESE G. Selective facilitation of responses to cortical stimulation of proximal and distal arm muscles by precision tasks in man. *J Physiol (Lond)* 491: 551–562, 1996.

SCHNEIDER C, DEVANNE H, LAVOIE BA, AND CAPADAY C. Neural mechanisms involved in the functional linking of motor cortical points. *Exp Brain Res* In press.

SCHNEIDER C, LAVOIE BA, AND CAPADAY C. On the origin of the soleus H-reflex modulation pattern during human walking and its task-dependent differences. *J Neurophysiol* 83: 2881–2890, 2000.

SCHNEIDER C, ZYTNICKI D, AND CAPADAY C. Quantitative evidence for multiple widespread representations of individual muscles in the cat motor cortex. *Neurosci Lett* 310: 183–187, 2001.

SCOTT SH. Role of motor cortex in coordinating multi-joint movements: is it time for a new paradigm? *Can J Physiol Pharmacol* 78: 923–933, 2000.

SHINODA Y, ARNOLD AP, AND ASANUMA H. Spinal branching of corticospinal axons in the cat. *Exp Brain Res* 26: 215–234, 1976.

SOECHTING JF. Effect of target size on spatial and temporal characteristics of a pointing movement in man. *Exp Brain Res* 54: 121–132, 1984.

TANTISIRA B, ALSTERMARK B, ISA T, KUMMEL H, AND PINTER M. Motoneuronal projection pattern of single C_3–C_4 propriospinal neurons. *Can J Physiol Pharmacol* 74: 518–530, 1996.

TOKUNO H AND TANJI J. Input organization of distal and proximal forelimb areas in the monkey premary motor cortex: a retrograde double labeling study. *J Comp Neurol* 333: 199–209, 1993.

ZIEMANN U, LONNECKER S, STEINHOFF BJ, AND PAULUS W. The effect of Lorazepam on the motor cortical excitability in man. *Exp Brain Res* 109: 127–135, 1996.