Direct Evidence for a Binding between Cognitive and Motor Functions in Humans: A TMS Study

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Abstract

■ During voluntary motor actions, the cortico-spinal (CS) excitability is known to be modulated, on the one hand by cognitive (intention-related) processes and, on the other hand, by motor (performance-related) processes. Here, we studied the way these processes interact in the tuning of CS excitability during voluntary wrist movement. We used transcranial magnetic stimulation (TMS) both as a reliable tool for quantifying the CS excitability, through the motor-evoked potentials (MEPs), and as a central perturbation evoking a movement (because the stimulation intensity was above threshold) with subjects instructed to prepare (without changing their muscle activation) either to "let go" or to "resist" to this evoked movement. We studied the simultaneous evolution of both the motor performance and the MEPs in the wrist flexor and extensor, separately for the successful trials (on average, 66% of the trials whatever the condition) and the unsuccessful trials; this allowed us to dissociate the intention- and performance-related processes. To their great surprise, subjects were found able to cognitively prepare themselves to resist a TMS-induced central perturbation; they all reported an important cognitive effort on the evoked movement. Moreover, because TMS only evoked short-latency MEPs (and no long-latency components), the amplitude of these short-latency MEPs was found to be related in a continuous way to the actual movement whatever the prior intention. These results demonstrate that prior intention allows an anticipatory modulation of the CS excitability, which is not only selective (as already known) but also efficient, giving the intended motor behavior a real chance to be realized. This constitutes a direct evidence of the role of the CS excitability in the binding between cognitive and motor processes in humans. ■

INTRODUCTION

Over the two last decades, there has been growing neurophysiological evidence, both in monkeys and humans, that cognitive and motor functions are so intimately linked that cognitive factors set neural activity in motor related cortical areas, even at the level of the primary motor cortex (see Georgopoulos, 2000; Requin, Brener, & Ring, 1991; Evarts, Shinoda, & Wise, 1984; Riehle, 2004, for reviews). Indeed, in monkeys, using single-cell recording and the movement-precueing method, it has been shown many times that a prior instruction provided to the animal about what he has to do modifies the activity of neurons in the motor cortex (without any change in muscle activation patterns) while the animal is waiting for the trigger signal (Crammond & Kalaska, 2000; Alexander & Crutcher, 1990; Georgopoulos, Lurito, Petrides, Schwartz, & Massey, 1989; Riehle & Requin, 1989). Moreover, using partial prior information about an upcoming movement task, it was found that the shape of preactivation patterns depends on the range of precued movement directions (Bastian, Riehle, Erlhagen, & Schöner, 1998). These many signatures of cognitive processes in the activation pattern of the primary motor cortex gave rise to the idea that the motor cortex is a crucial node in the processing of cognitive information related to motor functions.

Strong evidence of cognitive influences over the primary motor cortex has also been found in humans. Indeed, several brain imaging studies (using fMRI, PET, or EEG) conducted on movement simulation have shown that the primary motor cortex can be activated in the absence of any movement if the subject simply mentally simulates a movement (Grèzes & Decety, 2001; Porro et al., 1996), but of course much less than during the overt movement itself. Moreover, it has also been shown that the primary sensorimotor cortex is activated during movement preparation (Ball et al., 1999; Deiber, Ibanez, Sadato, & Hallett, 1996) with a tendency to be more active when some precueing information was present than when it was absent (Deiber et al., 1996).

Transcranial magnetic stimulation (TMS) has also been used to demonstrate the intermingling of cognitive and motor processes in the tuning of cortico-spinal (CS) excitability. Indeed, this technique offers a unique opportunity to enter within the cognitive–motor loop to test the CS excitability at different stages between the initial intention to the realization of a motor action.

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When looking at the cognitive–motor loop from the cognitive perspective, that is, without movement execution, CS excitability has been found to change selectively depending on the subject's intentions during motor preparation using go/no-go protocols (Hoshiyama et al., 1997), during mental movement simulation (Fadiga et al., 1999; Rossi, Pasqualetti, Techhio, Pauri, & Rossini, 1998; Kasai, Kawai, Kawanishi, & Yahagi, 1997) and even during movement observation (Fadiga, Fogassi, Pavesi, & Rizzolatti, 1995). In all these experiments, representations of action were studied in the absence of any movement (imagination, observation) or before the movement is performed (preparation), with the underlying hypothesis that the observed mechanisms do have some relationships with those involved in producing the overt movement (Jeannerod, 1995), but without being able to investigate this relationship.

Looking at the cognitive–motor loop from the motor perspective, that is, during movement execution, it has been demonstrated that CS excitability depends on the task performed by the subject, for upper limbs (Aimonetti & Nielsen, 2002; Schieppati, Trompetto, & Abbruzzese, 1996) as well as for lower limbs (Bonnard, Camus, Coyle, & Pailhous, 2002; Capaday, Lavoie, Barbeau, Schneider, & Bonnard, 1999). Indeed, selective modulations of motor-evoked potentials (MEPs) were observed when the same muscles activated at the same level were involved in different tasks [isometric wrist extension vs. a clenching movement (Aimonetti & Nielsen, 2002) and postural vs. precision tasks (Schieppati et al., 1996)]. Another important finding in this perspective is that the CS excitability is selectively modified by motor practice; presumably forming the neurophysio-logical basis for motor learning (Classen, Liepert, Wise, Hallett, & Cohen, 1998; Pascual-Leone et al., 1995). This strongly suggests a relation between CS excitability and movement efficiency (i.e., the fact that the overt movement becomes closer to the intended movement). From the above-mentioned TMS studies, it is impossible to address the question of the interaction between cognitive (intention-related) and motor (performance-related) processes in the tuning of the CS excitability during motor functions. Indeed, these processes have never before been dissociated in the same experiment.

In monkeys, this issue has already been investigated by the pioneering work of Evarts and Tanji (Tanji & Evarts, 1976; Evarts & Tanji, 1974). Indeed, they demonstrated for the first time an anticipatory activity of motor cortex neurons after a prior instruction telling the animal how to respond (either by pushing or by pulling) to a subsequent perturbation (delivered a few seconds later), which triggered the instructed movement. Interestingly, because these authors were inspired by Hammond's (1956) initial observations that an intention can profoundly modify even short-latency motor responses to kinesthetic input, they tackled the problem of anticipation using peripheral perturbation of the

movement. As in the aforementioned preparation studies, recordings in precentral sensorimotor cortex have revealed instruction-induced changes of neuronal activity during the period between the instruction and the perturbation–triggered movement. Moreover, they reported a correlation between the instruction's effect on neuronal discharge and the subsequent motor performance. Indeed, they used the very rare instances in which mistakes did occur to show that if a cell shows the ''wrong'' response to the prior instruction, the following perturbation elicits the ''wrong'' movement. Although informative, this latter result must however be taken with caution; as emphasized by Fromm (1986), even consistent temporal and parametric correlations as found in pretrained tasks cannot necessarily be taken to imply a functional relation between a neuron and a motor response.

To get a better idea of the interaction between cognitive (intention-related) and motor (performance-related) processes in the tuning of CS excitability in human beings, we performed an experiment in which subjects were engaged in the same motor task (they performed rhythmical flexion/extension movements of the wrist) but with two opposing cognitive attitudes (active/passive) with respect to potential perturbations, as in the studies of Evarts and Tanji (1974). However, in our case, the unpredictable selective perturbations were central, that is, induced by applying a TMS pulse over the primary motor cortex (Wagener & Colebatch, 1996). The intensity being 1.6 times above motor threshold, this TMS pulse evoked a movement that was superimposed onto the voluntary wrist movement. Compared to peripheral mechanical perturbations (Rothwell, Traub, & Marsden, 1982; Rothwell, Day, Berardelli, & Marsden, 1986; Evarts & Tanji, 1974), such central perturbations offer the unique opportunity to activate the descending motor tracts (CS tract among others) directly while shunting the ascending tracts assisting the movement. Thus, TMS was used both to centrally perturb the organization of movement and as a reliable tool for quantifying the CS excitability via the short-latency component of the MEPs (Gandevia & Rothwell, 1987). Indeed, this component is presumed to reflect the excitation of the cortical neurons from the fifth layer. Although the occurrence of the central perturbation in the sequence could not be predicted, the TMS-evoked movements were known by the subjects as always directed toward an increased flexion of the wrist and, according to the conditions, two opposite instructions were given to the subjects with respect to these evoked movements. As in the studies from Evarts and Tanji (1974), one instruction was to prepare to let the evoked movement be performed, that is, to ''let it go'' without voluntarily intervening to avoid it (passive subject); hereafter, this condition will be referred to as the nonintervention condition (NINT). Inversely, the other instruction was to prepare themselves, but only by

thinking (and not by coactivating their muscles), so that no evoked movement was observed at the wrist joint (active subject); hereafter, this will be referred to as the compensation condition (COMP). This latter instruction always required further motivation of the subjects, all of them initially believing that nothing could be done to attenuate a TMS-evoked movement.

Until now, the few studies that have used TMS as a central perturbation (e.g., Wagener & Colebatch, 1996) have never tried to vary the subject's cognitive states. Therefore, it is difficult to make any strong prediction about the capability of human subjects to cognitively compensate for the effects of a central perturbation induced by TMS. However, given that the studies about movement preparation (Hoshiyama et al., 1997) or mental movement simulation (Fadiga et al., 1999; Kasai et al., 1997) have shown that prior intention is able to induce a selective modulation of MEPs, we can reasonably expect some differences between MEPs in NINT and COMP conditions. This is further reinforced by the anticipatory activity found in motor cortex neurons when prior instruction is given to the animal telling him how to respond to a subsequent perturbation (Tanji & Evarts, 1976). The present experiment aimed to determine whether these expected modulations in MEPs relate to the overt behavior or rather to the subject's intention. As in the study by Tanji and Evarts (1976), the successful and unsuccessful trials were processed differently to distinguish between cognitive (intention-related) and motor (performance-related) processes in the tuning of CS excitability.

RESULTS

Movement Patterns

Figure 1 (top) shows the phase plane portraits of the 40 last stimulations observed in the two conditions in a typical subject. They were superimposed onto the nonperturbed cycles. It clearly appears that the deviations from the initial steady state induced by TMS observed in the NINT condition were compensated in the COMP condition.

Standard descriptive statistics were performed on the peak flexion observed for the stimulated cycles. After having verified normality of the distributions of peak flexion observed over the whole experiment and over

Figure 1. Top: Typical example of phase plane trajectories of moving wrist (in the displacement/velocity plane) observed in the NINT and COMP tasks, showing that indeed the instruction given to the subject (to let go/resist the TMS-evoked movement) influenced the motor performance. Nonperturbed cycles (indicating the initial steady state) are drawn in solid black lines and perturbed cycles (from 10 msec before to 300 msec after the TMS pulse) are drawn as dotted black and white lines. About 200 unperturbed cycles with 40 perturbed cycles in between have been represented. In the NINT condition, perturbed cycles clearly deviated with respect to nonperturbed cycles. By contrast, in the COMP condition, they stayed within the range of the nonperturbed cycles. For the x-axis, positive values represent extension and negative values represent flexion. Bottom: Averaged amplitude of the TMS-evoked movements (deviation of the average perturbed from the average nonperturbed movement) observed in the successful trials in each condition and each subject.
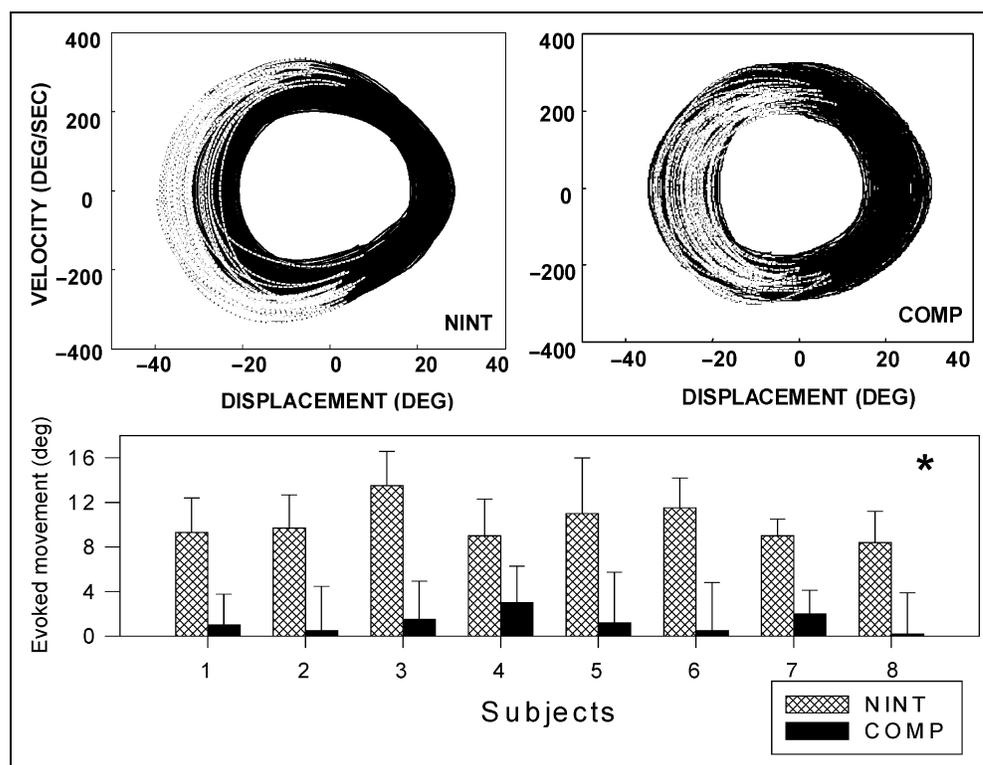
each condition ($p < .01$), the distributions of peak flexion in NINT and COMP conditions were compared and found to be significantly different ($p < .0001$). Moreover, based on the movement pattern, a criterion for task realization (i.e., performance) was adopted to distinguish between successful and unsuccessful trials. Based on the phase portrait presented in Figure 1, we determined the initial steady state for the unperturbed trials (average and normal fluctuations) as described by Kay, Saltzman, and Kelso (1991), then each stimulated cycle deviating from the initial steady state was considered as successful in the NINT condition and unsuccessful in the COMP condition. Inversely, each stimulated cycle staying within the initial steady state for the unperturbed trial was considered as successful in the COMP condition and unsuccessful in the NINT condition. Over the whole experiment, the mean percentage of successful trials was found to equal 66% in NINT and 67% in COMP. Figure 1 (bottom) presents the averaged amplitude of the TMS-evoked movement (i.e., deviation in peak flexion between perturbed and non-perturbed trials) observed for the successful trials in each condition in the different subjects. A two-way repeated measures ANOVAs conducted on the peak flexion observed at the stimulated cycle with factors task (NINT/COMP) and performance (successful/unsuccessful) yielded a significant interaction between the two factors, $F(1,7) = 39.2$, $p < .05$. Moreover, post hoc Newman–Keuls contrasts showed that for successful trials, the NINT and COMP conditions were significantly

different ($p = .005$), the peak flexion being greater in NINT (on average, by $10°$).

This first stage demonstrates that, to a certain extent, a subject is able to cognitively prepare him/herself to compensate for the effect of a TMS episode, the next step is now to investigate whether any change in the short-latency component of the MEPs (reflecting a change in the CS excitability) underlies this capacity of intentional motor preparation. Indeed, given that the electromyographic (EMG) response evoked by TMS comprises several components (Dimitrijevic et al., 1992; Edgley, Eyre, Lemon, & Millner, 1990), there can be, a priori, no univocal relationship between the short-latency MEPs and the evoked movement.

## MEPs in Flexor and Extensor Muscles

For none of the muscles, we observed long-latency components in the TMS-evoked EMG response. Therefore, only the short-latency component was analyzed. For both muscles, analyses were conducted both on absolute amplitude of these short-latency MEPs (for similar initial EMG backgrounds) and on normalized MEPs (ratio of MEP to background). Because the results did not differ, we only report the results for absolute MEPs. Figure 2B shows, for a typical subject, the mean MEP in the flexor muscle and the mean movement pattern observed in NINT and COMP conditions.

Standard statistics were done on MEPs amplitude (for similar EMG backgrounds) following the same

Figure 2. (A) Example of the raw EMG activity (mV) of the flexor (flexor carpi radialis) and extensor (extensor carpi radialis) muscles observed during several perturbed movement cycles preceding and following the stimulus (indicated by the arrow on the movement plot upper). On this graph, 40 successive perturbed movements (whatever the performance), observed in the NINT condition, were aligned with respect to the stimulation and superimposed to show the stability and the reproducibility of the MEPs. (B) Top: Averaged perturbed movement cycle (over the last 40 successive perturbed cycles in each condition, whatever the performance) observed in a typical subject in the NINT (dotted line) and COMP tasks (full line). Bottom: Averaged MEPs observed in the flexor muscle in the two experimental conditions in the same subject. Same legend as in the upper graph. The dotted vertical line indicates the moment of stimulation. Note that, to better visualize the instruction-related effects on the two signals, the time scale is not the same in the two graphs.
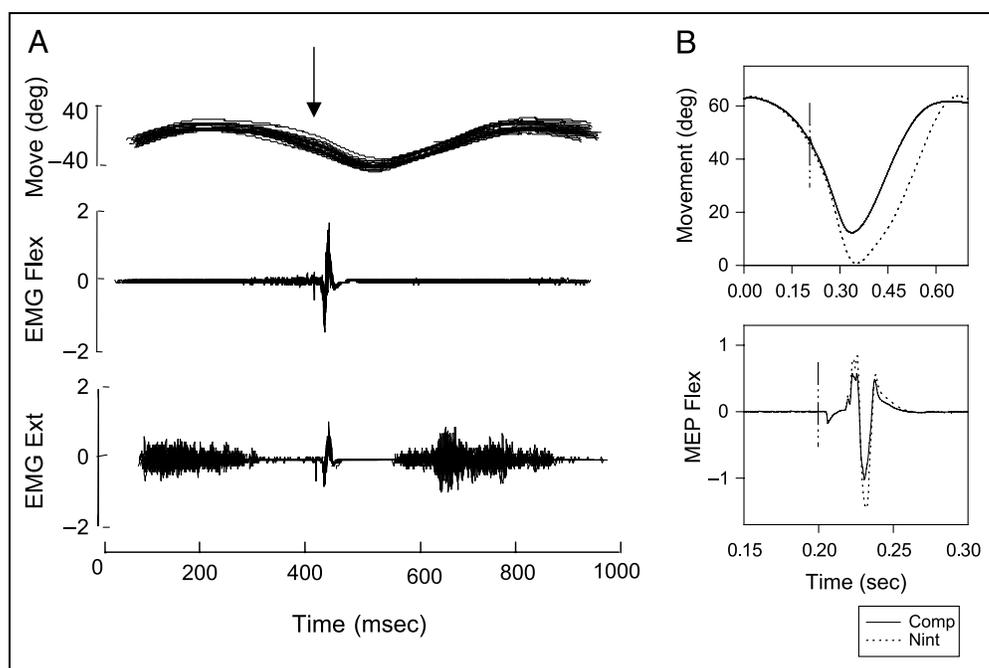
Figure 3. Left: Mean amplitude of MEPs observed in the flexor and extensor muscles (at similar EMG backgrounds) in the successful trials during the COMP and NINT conditions for each subject. Data from all subjects ($n > 50$ for both muscles) are presented. Right: Averaged MEPs amplitude observed in the flexor and extensor muscles in the different conditions for successful and unsuccessful trials. A significant interaction between task and performance was found for the flexor, but not for the extensor muscles.
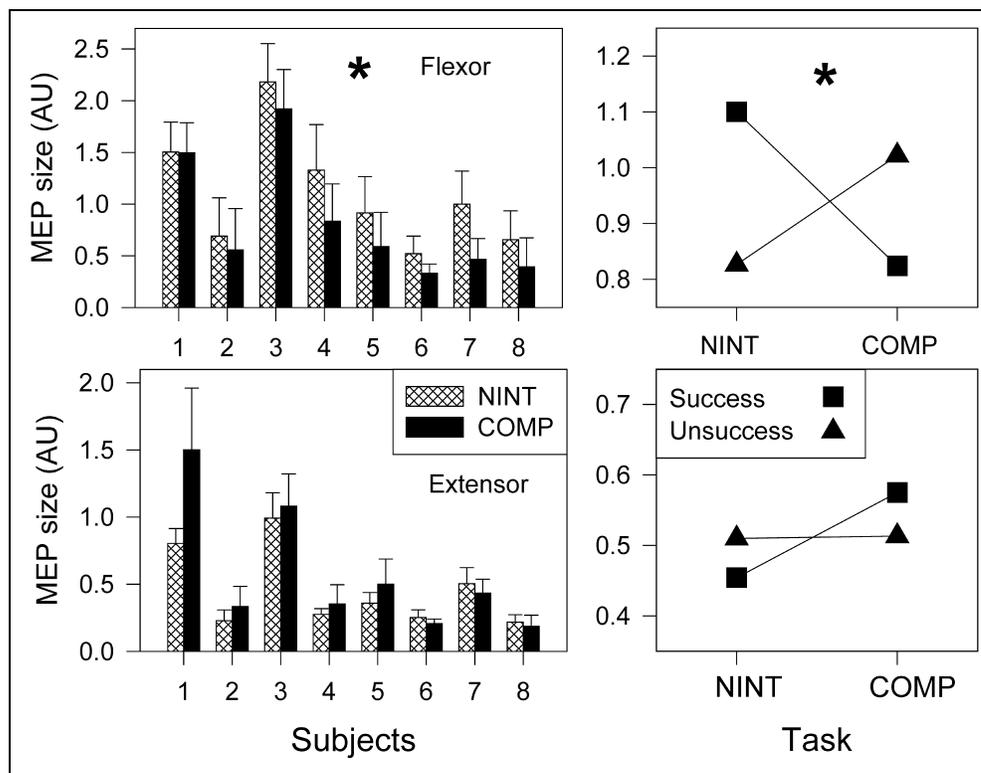
procedure as described above. We first verified normality of the distributions of the MEP amplitude of the flexor muscles (MEP-Flex) observed over the whole experiment and over each condition ($p < .01$). Then, the distributions observed in NINT and COMP conditions were compared and found to be significantly different ($p < .0001$). Moreover, the same criterion for task realization (based on the movement pattern) was adopted to distinguish between the MEPs amplitude observed in successful and unsuccessful perturbed cycles. Figure 3 presents the average MEPs observed in the flexor and extensor muscles during the successful trials for each subject. A two-tailed ANOVA performed over the whole experiment on the amplitude of MEP-Flex with factors task and performance yielded a significant interaction, $F(1,7) = 46.2$, $p < .05$, the MEP being modulated by the task but depending on the performance.

Figure 3 shows this interaction. Post hoc Newman–Keuls contrasts revealed that, for successful trials, the MEP-Flex was smaller for COMP than for NINT conditions ($p = .003$). By contrast, in the unsuccessful trials, the MEP-Flex was found to be greater for COMP than for NINT conditions ($p = .005$). Interestingly, the contrast also showed that MEP-Flex for unsuccessful trials in one condition were not significantly different from the successful trials of the other condition ($p > .1$), which shows that modulations of MEP-Flex are related to the performance (the actual movement) and not to the sub-

ject's intention itself (intended movement). Figure 4 presents a typical example of how the MEP-Flex correlates with the movement parameter in the NINT and COMP conditions, and the correlation was found the same whatever the condition.

The same procedures were followed for processing the MEP amplitude of the extensor muscles (MEP-Ext). However, two-tailed ANOVAs with factors task and performance did not yield any significant effect neither for the factors nor for their interaction (p always $> .05$). Figure 3 shows the averaged MEPs observed in the extensor during the successful trials in the two conditions for each subject. Except for Subject 1, the task-related differences were always smaller than for the flexor. Moreover, individual strategies were observed for this muscle: the MEPs being increased for five subjects and decreased for three others. It has to be noted that both of these strategies are valid because, when the TMS pulse occurs, the first strategy decreases/increases the flexor/extensor torque around the wrist joint while the second strategy decreases both but more the flexor than the extensor. Together, these two observations (smaller task-related difference in the extensor than in the flexor and the fact that either an increase or a decrease in the MEPs of the extensor muscle can be observed during the compensation of the TMS-evoked movement) suggest that, except for Subject 1, the compensation of the TMS-evoked movement was essentially realized by modulating the MEPs of
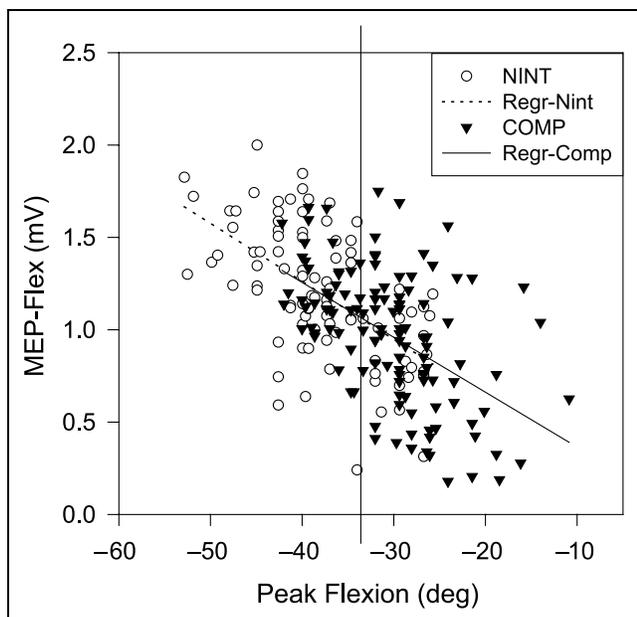
Figure 4. Amplitude of the MEP-Flex plotted against the peak flexion of the perturbed movements observed in a typical subject over the whole experiment, showing that MEP-Flex correlates with the overt performance. Each symbol corresponds to a stimulated cycle observed in the NINT (circle) and COMP (triangle) tasks. The regression lines are shown separately for the two tasks, but they are not different (NINT: $y = -0.031x + 0.005$, $R^2 = .329$, $p < .01$; COMP: $y = -0.030x + 0.068$, $R^2 = .265$, $p < .01$). The vertical solid line indicates the performance criterion, the task being successful/unsuccessful at the left/right of the line for the NINT task and successful/unsuccessful at the right/left of the line for the COMP task.

the flexor muscle, the extensor muscle playing a rather secondary role.

DISCUSSION

A remarkable result of this study is that, within a certain limit, and to their own great surprise, subjects were able to cognitively prepare themselves to compensate for a TMS-induced central perturbation; they all reported an important cognitive effort on the evoked movement such that they progressively succeeded to decrease or even to eliminate this movement. Moreover, it has to be noted that this preparation was achieved without any increase in EMG activity in the flexor and/or extensor muscles (this was monitored throughout the experiment and only the evoked movements with similar backgrounds for the two muscles were further analyzed). Indeed, such an increase in EMG activity is well-known to be an efficient way of organizing the compensation at the peripheral level (Abbs & Gracco, 1984; Feldman, 1980). From a methodological point of view, this emphasizes the importance of giving explicit instruction about what the subject has to do in TMS studies. Whether the subjects were engaged in the passive or in the active cognitive attitude, the percentage of successful trials was far above random, meaning

that the intention-related processes have indeed influenced the probability of observing the desired movement pattern (a TMS-evoked movement in the NINT condition, a smaller or even no evoked-movement in the COMP condition).

More generally, these results show how cognitive (intention-related) and motor (performance-related) processes interact in the tuning of CS excitability. Over the past 15 years, there has been much evidence showing that cognitive factors shape the activation of motor-related cortical areas, both nonprimary (McDowell, Jeka, Schöner, & Hatfield, 2002) and primary (see Georgopoulos, 2000; Requin et al., 1991; Riehle, 2004, for reviews). In line with this perspective, the present results clearly show that a prior intention selectively modifies the CS excitability. Indeed, in the successful trials, a task-specific modulation of MEPs was observed in the flexor muscles. Of course, this result is in agreement with the studies on movement preparation (Hoshiyama et al., 1997) and on movement simulation (Rossi et al., 1998) in which such a specific facilitation of MEPs was observed in the agonist muscle acting as "prime mover" when subject mentally simulated either a wrist flexion or extension. Moreover, the study by Kasai et al. (1997) showed that such an increased facilitation of the MEPs in the wrist flexor during motor imagery of wrist flexion occurred without any change at the level of spinal excitability, suggesting that the changes occurred at the cortical level.

Furthermore, the present experiment demonstrates that these selective intention-related modulations in CS excitability allow the intention to be realized (i.e., are efficient). Indeed, for the first time, we were able to distinguish between cognitive- and motor-related factors in the modulations of CS excitability accompanying the motor function. Thus, the interaction found between motor performance (successful or unsuccessful) and prior intention (nonintervention vs. compensation) in determining the amplitude of MEPs leads us to suggest that the observed modulations of MEPs are related to the motor performance, and even underlie it, as also suggested by the correlation between motor performance and MEPs. It has to be remembered that, given that the EMG response evoked by TMS is composed of several components (Dimitrijevic et al., 1992), there can be, a priori, no univocal relationship between the short-latency MEP and the TMS-evoked movement. However, in the present experiment, no long-latency responses were observed, and thus, the performance only depended on the short-latency MEPs). Thus, our results show that a motor intention does indeed influence the CS excitability only if it is going to be realized. Therefore, the CS excitability appears to be related to the intention realization (i.e., the binding of cognitive and motor processes) rather than to the intention itself (i.e., cognitive processes alone). Moreover, this strongly suggests that the tuning of CS excitability forms the mean of transforming a prior intention into its realization.

Of course, this does not exclude the possibility that pure intention could also be present at the level of the primary motor cortex, as suggested by Riehle and Requin (1989) who found ''pure'' preparatory neurons at the level of the primary motor cortex, albeit in lower percentage than in the premotor cortex and supplementary motor area. Indeed, as mentioned in the Introduction, the TMS technique only allows to test the excitability of the CS tract as a whole (i.e., including the motor cortical circuitry, segmental interneurons, and the α-motor neurons, being unable to attribute any change in the whole to a change in one or the other of the elements). Therefore, it reflects in general terms the functional linkage of the motor cortex and the segmental circuits activated by the CS tract (Capaday et al., 1999). Saying that this global excitability is related to the realization of the action does not exclude the possibility that superficial layers of the motor cortex (above the fifth layer) are influenced by purely cognitive processes. Indeed, the capability of these superficial layers to exert excitatory or inhibitory influence on the CS neurons has been demonstrated using the double-pulse technique (Di Lazzaro et al., 1998).

In any case, the cortical origin of the processes (inhibitory processes over the flexor or excitatory/inhibitory over the extensor) allowing to bypass (at least partly) a TMS pulse remains to be proven. However, to our opinion, at least two main findings could argue in favor of this hypothesis concerning the involvement of motor cortex in such a compensation. The first comes from the studies by Evarts and Tanji (Tanji & Evarts, 1976; Evarts & Tanji, 1974), who described an anticipatory activity of motor cortex neurons when an animal is supposed to respond (by pushing or pulling) to a subsequent peripheral perturbation. Moreover, this activity seemed to be associated with the correct behavioral response. In the case of a TMS-induced central perturbation, one can suppose that such an anticipatory activation of motor cortex neurons is still more likely because it would allow a reduction of the effects of the central perturbation at its origin. The second argument lies in the fact that, in our experiment, the TMS-evoked movement was superimposed onto a voluntary rhythmical movement. Therefore, one can suppose that if inhibitory processes were acting at the spinal level (as in the preparation studies from Prut & Fetz, 1999), they would interfere with the voluntary movement.

These results are of interest because they lead us to propose that the modulation of CS excitability observed during motor imagery (Kasai et al., 1997; Rossi et al., 1998; Fadiga et al., 1995) really has a functional meaning related to the motor output. Indeed, in the present experiment, we did not find any intention-related difference in MEPs between unsuccessful trials of one condition and the successful trials of the other condition (in which the motor performance was the same but the prior intention differed). Therefore, in a sense, these results explain why motor simulation (mental training) is able to increase, within certain limits, the capability of acquisition of new simple motor skills (Maring, 1990). Indeed, in simple cases (as it is often the case in laboratory studies on motor preparation, simulation, or observation), the intention to act is intimately linked to the motor mechanisms, allowing this intention to be realized. Therefore, the same modulations of CS excitability are observed when imagining and when executing the movement and they are related to the overt motor performance. However, in more complex cases (and in nonexpert subjects), in which the intention to move is not so tightly related to the motor mechanisms allowing the intention to be realized, one can propose, based on the present results, that the modulation of CS excitability is related to the overt performance and not to the intended movement. Therefore, in such complex cases, the mental simulation or observation does not really lead to an improved performance.

In conclusion, this study aimed to understand the interaction of cognitive and motor factors in determining the modulations of CS excitability accompanying the voluntary motor functions. By using a central perturbation, it was shown that, at the behavioral level, cognitive factors (prior intention of being active/passive) influence the probability of observing the desired movement, and, at the same time, that, at the neurophysiological level, the amplitude of the short-latency component of the MEPs is related in a continuous way on the actual movement whatever the prior intention. This demonstrates that prior intention allows an anticipatory modulation of the CS excitability that is not only selective (as already known) but also efficient, giving the intended motor behavior a real chance to be realized. Therefore, these results constitute a direct evidence of the role of the CS excitability in the binding between cognitive (intention-related) and motor (performance-related) processes in humans.

METHODS

Subjects

This study was done on 10 healthy right-handed human subjects ranging in age between 22 and 38 years. All subjects gave their consent after being informed of the nature and procedure of the experiments. Care was taken to screen for any history of seizures or neurosurgery and for metal or electronic implants. The study was approved by the local ethics committee (CCPPRB Marseille 1, DGS 990460) in accordance with the Declaration of Helsinki.

Procedure

The subjects were seated in a comfortable armchair. The distal end of their forearm was immobilized horizontally

in an anatomical shaped device fixed with Velcro straps to ensure that the same position was maintained throughout the experiment, leaving the wrist joint free and maintaining the hand in a semiprone position. The experiment consisted of two main sessions. For both sessions, subjects were asked to produce a stable rhythmical flexion/extension movement at the wrist while keeping the same EMG activation pattern. They were told that sometimes TMS would be applied inducing movement perturbations in the direction of an increased flexion. In one session, subjects were asked to let the movement be clearly perturbed, that is, not to intervene voluntarily to avoid any TMS-induced effects (NINT). In the other session, subjects were asked to prepare themselves, but only by thinking (and not by coactivating their muscles), so that no movement perturbation induced by TMS would be observed at the wrist joint (COMP). At the beginning of the experiment, the movement frequency and amplitude were selected for each subject based on what is the most comfortable for the wrist oscillation. Then, throughout the experiment, an auditory metronome imposed the selected frequency. The subjects were asked to return comfortably to this frequency after each stimulation. For the amplitude control, subjects had a continuous on-line visual feedback of the last 5 sec of the wrist angular displacement on a PC computer screen, and two horizontal lines indicated the maximal flexion and extension angles that he/she had chosen at the beginning of the experiment. This allowed (1) to avoid any drift in their normal movement patterns in the unperturbed movements and (2) to allow an on-line evaluation of their performance when perturbed by TMS. Throughout the experiment, the experimenter evaluated the performance and encouraged the subjects. Moreover, the experimenter monitored the EMG patterns. In case of any visible change, he asked the subjects to regain the former level.

The order of the sessions was counterbalanced, five subjects began with NINT session and five with COMP session. According to the subjects and the conditions, between 120 and 160 stimulations were applied in each session. Indeed, we wanted to give each subject the most chances as possible to realize the different tasks but staying within the limits of his/her comfort and attentional resources (which varied among subjects). Moreover, because it was more difficult to avoid a TMS-evoked movement than to ''let go,'' more trials were conducted in the former condition. To avoid fatigue, each session was divided into several sequences (three to five according to the subjects). Between sequences and sessions, the subject had a few minutes of rest.

Magnetic Stimulation

Transcranial magnetic stimuli were applied over the scalp to the left motor cortex using a Magstim-200 stimulator (maximum magnetic field strength of 1.7 T,

Magstim, Dyfed, UK) using a focal double-cone coil (outside diameter 110 mm, with an induced current flowing in posterior–anterior direction). The Magstim-200 stimulator produces a damped, monophasic electric field, about 150 μs in duration. The subjects wore a latex swimming cap and surface markings were then drawn onto the cap to serve as a reference grid against which the coil was positioned. Throughout the experiment, the coil was held by an experimenter checking repeatedly to ensure that the position and orientation remained constant; this procedure evoked stable and reproducible responses (see Figure 2a). The coil was positioned over the left hemisphere, such that the central point between the loops was about 2 cm anterior and 6 cm lateral of the vertex (Cz), according to the 10–20 system for EEG electrode placement. The handle was always oriented such that the current flowed clockwise in the more lateral loop and counterclockwise in the more central loop. For each subject, fine adjustments of coil position were made at the beginning of the experiments to identify the optimal locations for evoking MEPs in the wrist flexor and extensor muscles of the right arm without uncomfortable effects in facial muscles. Keeping the coil at this optimal location, the intensity of the stimulation was slowly increased until the stimulation induced noticeable changes in the movement pattern (from 40% to 50% of maximal stimulator output according to the subjects). Throughout the experiment, this intensity was maintained. TMS triggering was achieved with a fixed delay following the wrist extension peak through a Pentium PC, which processed on-line the signal from the wrist goniometer, sampled at 1 kHz by a 16-bit A/D board using a Labview program (National Instrument). The program was designed to trigger stimulation every 7 ± 2 movement cycles. The variation (2) was introduced to avoid prediction. For each subject, at the beginning of the experiment, the stimulation delay was chosen to correspond to about 50% of the duration of the flexion movement, so that it always perturbed the ongoing wrist movement in the direction of an increased flexion peak.

Data Acquisition and Analysis

Bipolar EMG recordings from the flexor carpi radialis and extensor carpi radialis were obtained from pairs of surface disk electrodes placed over the belly of the muscle below the motor point. The electrodes were connected to an isolated preamplifier (gain 100). The ground reference electrode was placed on the styloid process of the ulna. The EMG signals were then amplified with appropriate gains and further filtered (band-pass: 30 Hz to 5 kHz). An electrogoniometer (Biometrics) was placed over the right wrist to measure the flexion/extension angles of the joint. It was calibrated at the beginning of the experiment and initialized in such a way that 0 corresponded to 180° at the wrist joint; flexion

corresponding to negative values. All signals were sampled continuously at 4 kHz using the SC/ZOOM data acquisition system (Department of Physiology, University of Umeå, Sweden).

The data were processed off-line. For each movement cycle in which TMS was applied, the following parameters were calculated: the background EMG, the peak-to-peak MEP-Flex and -Ext, the normalized MEP amplitude (ratio of MEP to background) for each muscle, and the maximum flexion angle of the wrist (peak flexion). Background EMG was computed as the averaged rectified EMG level over a 50-msec time window preceding the stimulus artifact. MEP-Flex and -Ext were defined as the difference between the lowest and highest value of the raw EMG signal (see Figure 2A) within the time window of 20–50 msec after the stimulus artifact.

For each muscle, MEPs were compared between the NINT and COMP conditions. However, since MEP changes as a function of the background EMG, in each subject, the mean size of the MEPs was compared only for trials explicitly selected so that the mean background EMG was not statistically different in the two tasks. The criterion for MEPs selection for the statistical analyses was that, for each subject, the background EMG fell within the common range for the two tasks (Schieppati et al., 1996).

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