◆ Human Brain Mapping 32:1471–1482 (2011) ◆

Contribution of the Primary Motor Cortex to Motor Imagery: A Subthreshold TMS Study

Barbara Pelgrims,[1] Nicolas Michaux,[2] Etienne Olivier,[1] and Michael Andres[1,2]*

[1]*Université catholique de Louvain, Institute of Neuroscience, Laboratory of Neurophysiology, Brussels, Belgium*
[2]*Université catholique de Louvain, Institut de Recherche en Sciences Psychologiques, Louvain-la-Neuve, Belgium*

Abstract: Motor imagery (MI) mostly activates the same brain regions as movement execution (ME) including the primary motor cortex (Brodmann area 4, BA4). However, whether BA4 is functionally relevant for MI remains controversial. The finding that MI tasks are impaired by BA4 virtual lesions induced by transcranial magnetic stimulation (TMS) supports this view, though previous studies do not permit to exclude that BA4 is also involved in other processes such as hand recognition. Additionally, previous works largely underestimated the possible negative consequences of TMS-induced muscle twitches on MI task performance. Here we investigated the role of BA4 in MI by interfering with the function of the left or right BA4 in healthy subjects performing a MI task in which they had to make laterality judgements on rotated hand drawings. We used a subthreshold repetitive TMS protocol and monitored electromyographic activity to exclude undesirable effects of hand muscle twitches. We found that BA4 virtual lesions selectively increased reaction times in laterality judgments on hand drawings, leaving unaffected a task of equal difficulty, involving judgments on letters. Interestingly, the effects of virtual lesions of left and right BA4 on MI task performance were the same irrespective of the laterality (left/right) of hand drawings. A second experiment allowed us to rule out the possibility that BA4 lesions affect visual or semantic processing of hand drawings. Altogether, these results indicate that BA4 contribution to MI tasks is specifically related to the mental simulation process and further emphasize the functional coupling between ME and MI. *Hum Brain Mapp 32:1471–1482, 2011.*

Key words: motor representations; proprioception; mental rotation; rTMS; laterality

INTRODUCTION

The numerous resemblances between overt and covert movements, such as their time courses and the similitude of physiological responses they trigger [Papadelis et al., 2007], suggested that movement execution (ME) and motor imagery (MI) share several mutual processes [Collet et al., 2000; Johnson, 2000; Papadelis et al., 2007; Parsons, 1994; Stevens, 2005]. This view is further supported by the large overlap between the brain areas recruited during both ME and MI as demonstrated by functional imaging studies [Ehrsson et al., 2003; Gerardin et al., 2000; Lotze et al., 1999]. However, the involvement of the primary motor cortex (Brodmann area 4, BA4) in MI, and its possible hemispheric dominance, are still a matter of debate.

Contract grant sponsors: the "Actions de Recherche Concertées" of the Communauté française de Belgique (ARC 07/12-007), the "Fonds Spéciaux de Recherche" (FSR) of the Université catholique de Louvain, the "Fonds de la Recherche Scientifique Médicale" (FRSM), the "Fondation Médicale Reine Elisabeth" (FMRE), and the "Fonds National de la Recherche Scientifique" (FRS-FNRS).

*Correspondence to: Michael Andres, Institute of Neuroscience, Laboratory of Neurophysiology, Université catholique de Louvain, Avenue Hippocrate, 54, B-1200 Brussels, Belgium.
E-mail: michael.andres@uclouvain.be

Received for publication 26 April 2010; Accepted 14 June 2010
DOI: 10.1002/hbm.21121
Published online 12 November 2010 in Wiley Online Library (wileyonlinelibrary.com).

First, experimental evidence for the involvement of BA4 in MI remains contradictory. Indeed, whereas some neuroimaging studies have found an increase in BA4 activation during MI [Ehrsson et al., 2003; Lacourse et al., 2005; Lotze et al., 1999; Porro et al., 1996; Sharma et al., 2008], others have failed to replicate these results [Gerardin et al., 2000; Stephan et al., 1995]. However, because fMRI is by definition a correlative technique, it does not permit, on its own, a determination of the causal role of a given area in the task at hand. Consistently with the conclusions of some neuroimaging studies showing an increased activation in BA4 during MI, previous transcranial magnetic stimulation (TMS) studies have demonstrated that MI is accompanied by an increased corticospinal (CS) excitability of the muscle(s) involved in the simulated movements [Fadiga et al., 1999; Pelgrims et al., 2005; Stinear et al., 2006; Yahagi and Kasai, 1998]. However, it is noteworthy that an increase in CS excitability, as estimated with TMS, may also originate from any nonprimary motor area connected to BA4 and/or directly to the spinal motoneurons [Fadiga et al., 2005].

The issue of the involvement of BA4 in MI has also been addressed by using TMS to interfere transiently with its function in subjects performing an MI task. Although most of these studies have reported a disruptive effect of BA4 virtual lesions on mental rotation of hand drawings [Ganis et al., 2000; Tomasino et al., 2005], their conclusions remain questionable because they have used a supra-threshold TMS, making it impossible to exclude that the MI deficits were not a side effect of hand movements induced by TMS. This criticism is particularly important when considering the influence of proprioception on MI performance [Parsons, 1994; Sirigu and Duhamel, 2001; Vargas et al., 2004].

Another critical issue when discussing the contribution of BA4 to MI is to determine the precise function of this area in processes underlying MI. Because the results of previous TMS studies showing a causal relationship between BA4 and MI were gathered in tasks which rely on the visual processing of hand drawings, we cannot exclude the possibility that BA4 is involved in the perception of hand posture and/or in accessing the meaning of these postures [Ganis et al., 2000; Tomasino et al., 2005]. Understanding the role of BA4 in MI tasks also requires clarifying the hemispheric lateralization of MI processes. Indeed, most neuroimaging studies reported a bilateral activation of BA4 during MI of whichever hand was involved in the simulated movement [Creem-Regehr et al., 2007; Lacourse et al., 2005; Lotze et al., 1999; Parsons, 1998; Vingerhoets et al., 2002], whereas others suggested a left hemispheric lateralization [Kosslyn et al., 1998; Tomasino et al., 2005]. Should the left hemispheric dominance be confirmed, it is necessary to assume that BA4 contributes to a central process underlying MI, such as inferring the meaning of a given hand posture.

The aim of this study was to gain further insight into these different issues. To do so, we used a subthreshold TMS intensity to induce virtual lesions of BA4, after determining carefully the motor threshold by using electromyographic recordings (EMG). In a first experiment, we used a task in which participants had to judge whether a hand drawing displayed from different viewpoints and rotation angles represented either a left or a right hand. Such a task has been consistently proved to involve mental simulation of hand movements [Parsons, 1987b; Sekiyama, 1982; Thayer and Johnson, 2006] and to be influenced by the same motor constraints (e.g. biomechanical limitations) as ME [Parsons, 1987a,b, 2001; Pelgrims et al., 2009; Petit et al., 2003]. Moreover, because mental rotation remained implicit in this task, it also allowed us to overcome the possible limitations related to the use of different strategies by participants [Johnson, 2000]. Finally, another advantage of this task is the possibility to run a control experiment strictly under the same conditions but with different stimuli in order to separate the specific effects of TMS on mental imagery. In order to discriminate between alternative interpretations regarding the role of BA4 in MI, we conducted a second experiment in which participants were asked to name the red-outlined digit on a right or left hand drawing displayed in a canonical orientation so that the only requirement was to process the hand drawing and to recognize a given finger.

EXPERIMENT 1

Materials and Methods

Subjects

Twelve healthy volunteers (all males, age: 27.8 ± 2.3 years, mean ± SD) participated in Experiment 1. They were all right-handed according to the Waterloo Handedness Questionnaire [Steenhuis and Bryden, 1989] and had no history of neurological disease; their vision was normal or corrected to normal. All subjects were screened for the potential risks of TMS by using the TMS adult safety screen questionnaire [Keel et al., 2001]. They were paid for their participation and gave written informed consent. The experimental procedures were approved by the local Ethics committee of the Université catholique de Louvain and the study conforms with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Task Description

Subjects were seated comfortably in an armchair in front of a computer screen located at a distance of 60 cm; their arms were flexed with the forearms lying on a pillow and their hands half-pronated in a relaxed position. The MI task consisted in deciding whether a black line-drawing of a hand presented on the computer screen represented a right or a left hand [Parsons et al., 1995]. Subjects had to respond verbally by saying “gauche” (left) or “droite” (right). In the control Letter task, the stimulus was a letter presented either in its canonical or in its mirror form and subjects had to determine whether the letter was in its canonical form. They responded verbally by "oui" (yes) or "non" (no).

Stimuli had a maximum size of 5° and were displayed using E-Prime software [Psychological Software Tools, 2002, Pittsburgh), on a white background. Figure 1 illustrates the sequence of events occurring in a trial: a central cross was displayed for 200 ms, followed by a 500 ms delay and then by the stimulus (a hand drawing or a letter), also displayed for 500 ms. The experimenter made a note of the verbal responses which were analyzed off-line in order to eliminate error trials. Reaction time (RT) was measured on-line by means of a voice key connected to E-prime.

In the MI task, the stimuli were five right and five left hand drawings presented from different viewpoints (a palm view, a back view, a side view, a thenar/hypothenar eminence view and a front view of the finger tips; see Fig. 1). In the control task, the stimuli were five letters (J, N, S, Z, and G) presented either in a canonical or a mirror form. In both tasks, the stimulus was presented at one of the following rotations: 30°, 90°, 150°, 210°, 270°, or 330° clockwise. Therefore, there were 60 different possible stimuli for the MI task (five hand postures × two laterality (left/right) × six orientations) and 60 for the Letter task (five letters × two representations (canonical/mirror) × six orientations). These stimuli were carefully selected on the basis of a pilot study so that both tasks were comparable in terms of difficulty, as estimated by the RT. Three separate t-tests performed on the no-TMS trials confirmed that the MI and Letter tasks were equivalent in terms of RT (mean RT, MI: 940 ms, letter: 967 ms, $t(11) < 1$), SD (MI: 228 ms, letter: 227 ms, $t(11) < 1$) and error rate (MI: 5.4%, letter: 3.7%, $t(11) < 1$).

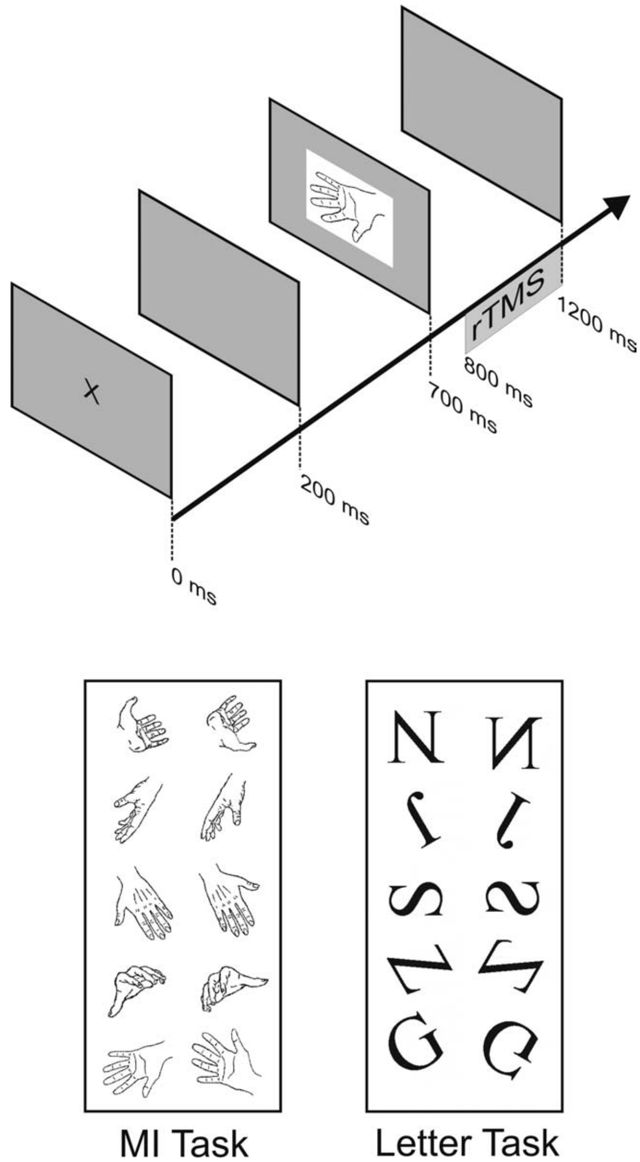

Figure 1.
Time course and schematic view of the MI and Letter tasks (Experiment 1). The insets show the stimuli used in each task.

Transcranial Magnetic Stimulation

In order to increase the likelihood of perturbing the process performed by BA4 during MI, we used repetitive TMS (rTMS) rather than single pulse TMS. rTMS was delivered with a Rapid Magstim model 200 stimulator (Magstim Company, Dyfed, UK) through a 70 mm external diameter figure-of-eight coil placed over the hand area of the left or right BA4. The coil was held tangential to the skull with the handle pointing laterally and backwards. The "hot spot" was defined as the location where a single TMS pulse elicited the largest EMG response observed in the Flexor Carpi Radialis (FCR) of the contralateral hand. Participants wore a tight-fitting EEG cap taped to the scalp. The resting motor threshold (rMT), defined as the lowest TMS intensity which elicited 5 motor evoked potentials (MEPs) of about 50 μV in a series of 10 stimulations [Rothwell et al., 1999], was determined for each side. The rMT did not differ for the left (52% of the maximum stimulator output) and right hemispheres (54%, paired t-test: $t(11) = -1.61$; $P > 0.05$). We kept track of the coil position over the hotspot by putting one mark on the EEG cap in front of the coil and two marks laterally, in the inner parts of the two wings. The coil was held tangentially to the scalp by the experimenter and the marks were used to ensure the same placement throughout the experimental blocks. The TMS intensity was set at 90% of the rMT of the corresponding hemisphere in order to reduce the likelihood of eliciting MEPs. During the tasks, a 400 ms rTMS train (5 pulses, 10 Hz) was delivered 100 ms after the onset of the stimulus (hand or letter) presentation. Trains were separated by at least 6 s in order to respect the

TABLE I. Mean (±S.D.) RMS (μV) in the left and right FCR during the MI and Letter tasks for each TMS condition (experiment 1)

Hand	Task	No TMS	Left TMS	Right TMS
Left FCR	MI	0.0123 ± 0.0031	0.0119 ± 0.0024	0.0115 ± 0.002
	Letter	0.0119 ± 0.0019	0.0122 ± 0.0032	0.0116 ± 0.002
Right FCR	MI	0.0092 ± 0.0029	0.0088 ± 0.0019	0.0085 ± 0.0022
	Letter	0.0088 ± 0.002	0.008 ± 0.0015	0.0089 ± 0.0015

guidelines for the use of rTMS [Wassermann, 1998]. In the no-TMS trials, the coil was held over the left hotspot in half of the trials and over the right hotspot in the other half, but no TMS was delivered. EMG signals were recorded from the FCR with surface electrodes and were amplified (gain: 1000), high-pass filtered at 30 Hz (Neurolog, Digitimer, UK) and digitized on-line at 2 kHz using a CED 1401 interface (Cambridge Electronic Design, Cambridge, UK) connected to a personal computer. The FCR was chosen because of its involvement in the hand movements simulated in the MI task, the modulation of BA4 excitability during MI being muscle specific [Fadiga et al., 1999; Yahagi and Kasai, 1998]. For each trial, the EMG signal was acquired over a time period spanning 200 ms before TMS to 500 ms after the stimulus presentation.

Experimental Design

The experiment was conducted in a single session and half of the subjects performed the MI task first, followed by the Letter task; the order was reversed for the other subjects. For each task, three different TMS conditions were tested: (1) rTMS applied over the right BA4, (2) rTMS applied over the left BA4, (3) a no-TMS condition, used as a baseline. The order of these three TMS conditions was counter-balanced across subjects. Altogether, one experiment consisted of six blocks (two tasks × three TMS conditions).

Each no-TMS block included the 60 different stimuli (five hands or five letters × two responses × six orientations); each TMS block contained the same 60 stimuli but half of them were used twice in order to have a total of 90 trials per block. Each block was composed, for the six orientations, of an equal number of stimuli representing a right or a left hand (HAND SIDE) or showing the letter in its canonical or mirror form (LETTER FORM). In each block, the stimuli were presented pseudorandomly so that a given letter/hand drawing or response never occurred more than three times in a row. Before the TMS session, subjects performed 60 practice trials for each task.

Data Analysis

The following trials were discarded from the analyses: error trials (MI: 4.06%, letter: 3.68%), trials in which the verbal response was inaudible (MI: 0.54%, letter: 0.31%), trials with an RT falling outside the range of the mean individual RT ± 2 SD (MI: 4.34%, letter: 4.37%) and trials with an EMG activity larger than 50 μV during rTMS (MI: 14.1%, letter: 11.04%). Indeed, although we used a subthreshold TMS intensity, MEPs were sometimes elicited in certain trials. The disruptive effects of the BA4 virtual lesions were investigated on the remaining trials (MI: 77.74%, letter: 81.07%), by means of an ANOVA with TASK (MI vs. letter) and TMS (left, right or no-TMS) as within-subject factors.

Moreover, an ANOVA on the RT gathered during the MI task was performed with TMS, HAND POSTURE (five hand postures), HAND SIDE ("droite" vs. "gauche") and ORIENTATION (30°, 90°, 150°, 210°, 270°, and 330°), as within-subject factors in order to determine whether the mental rotation of hands complied with the biomechanical constraints, as classically observed in MI studies [Johnson, 2000; Sirigu and Duhamel, 2001]. In addition, this ANOVA allowed us to examine whether the effects of BA4 virtual lesions were dependent on the stimulus orientation. The same issue was investigated for the Letter task by mean of an ANOVA with TMS and ORIENTATION as within-subject factors.

Finally, in order to rule out that the effects of TMS reported in the present study were due to a difference in background EMG activity in the two tasks, two separate ANOVAs with TASK and TMS as within subject-factors, were performed on the root mean square (RMS) of the EMG signal recorded from the right and left FCR during a period of 200 ms before the TMS. These analyses showed that the background EMG activity was identical in all experimental conditions (all P-values >0.1; see Table I).

When appropriate, post-hoc comparisons were performed using Tukey corrected t tests ($\alpha = 0.05$).

RESULTS

We found a main effect of TMS ($F(2.22) = 7.084$, $P < 0.004$) and a significant TASK x TMS interaction ($F(2.22) = 9.261$, $P < 0.001$) on RT. Although the RT was not influenced by TMS in the Letter task ($F(2.22) = 1.036$, $P > 0.1$), in the MI task we found that TMS significantly affected the RT ($F(2.22) = 22.768$, $P < 0.001$; see Fig. 2). Post-hoc comparisons showed that, in the MI task, the RT increased significantly following either a left (1043 ± 262 ms, $t(11) =$

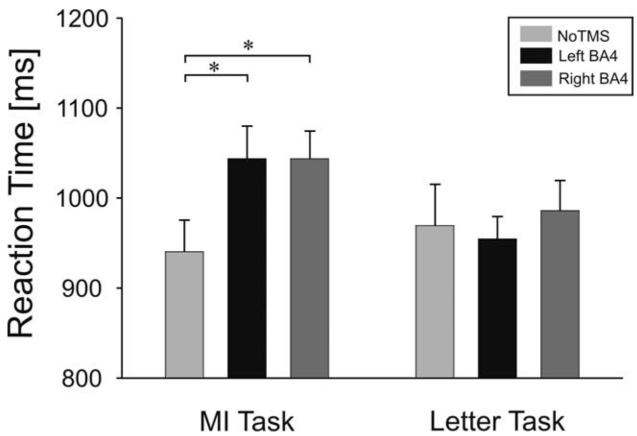

Figure 2.
Mean RT as a function of the task and the TMS conditions (Experiment 1). Asterisks indicate a significant difference between trials with a left or a right BA4 virtual lesion and trials without TMS ($P < 0.05$). Error bars represent the within-subject standard error of the mean [Loftus and Masson, 1994].

8.321, $P < 0.001$) or a right BA4 virtual lesion (1042 ± 253 ms, $t(11) = 8.207$, $P < 0.001$) when compared with the no-TMS condition (940 ± 235 ms). No RT differences were found between the left or right BA4 TMS conditions ($t < 1$).

The ANOVA with TMS, HAND POSTURE, HAND SIDE, and ORIENTATION as within-subject factors performed on the RT data gathered in the MI task confirmed the aforementioned results: there was a specific increase in RT only in the MI task following either a right or left BA4 lesion ($F(2.22) = 23.027$; $P < 0.001$). Moreover, we found a main effect of HAND POSTURE ($F(4.44) = 10.422$; $P < 0.001$), indicating that the drawings showing a front view of the finger tips led to longer RTs than the four other views (all $P < 0.001$). Additionally, as classically reported in the literature (e.g. [Maruff et al., 1999]), we found a main effect of HAND SIDE ($F(1.11) = 10.785$; $P < 0.007$) demonstrating that subjects responded faster when presented with a right hand (986 ± 255 ms) than with a left hand (1038 ± 245 ms). Finally, a main effect of ORIENTATION ($F(5.55) = 14.483$; $P < 0.001$) and a significant interaction between HAND POSTURE, HAND SIDE and ORIENTATION ($F(20.220) = 4.821$; $P < 0.001$) were also found. This three-way interaction indicated that the RT was influenced by the biomechanical constraints in a specific manner for each posture of the right and left hands (see Fig. 3). For instance, since hand adduction can be performed over a larger angular distance than abduction, mental rotation of a right hand in a back view (Fig. 3A) should be more limited counter-clockwise than clockwise, and vice-versa for left hands. Our results confirmed this prediction and we found that mental rotation of a right hand in a back view was more time consuming when presented with an orientation of 210° than 30° ($F(11.55) = 3.469$, $P < 0.009$; $t(6) = 5.075$, $P < 0.009$), whereas for left hand pictures, it was slower when presented at an angle of 150° than at 30° ($F(11.55) = 3.389$, $P < 0.01$; $t(6) = 4.355$, $P < 0.036$). As illustrated in Figure 3, distinct relationships between RT and the angle of rotation were systematically found for the right and left hands and for the different postures, consistently with the biomechanical constraints specific for each hand posture. Importantly, we failed to find an interaction between TMS and HAND POSTURE, HAND SIDE or ORIENTATION indicating that the effects of BA4 virtual lesions were independent of these factors.

The ANOVA performed on the RT data gathered during the Letter task with TMS and ORIENTATION as within subject-factors showed a main effect of stimulus ORIENTATION ($F(5.55) = 9.853$, $P < 0.001$). Trend analyses revealed a curvilinear relationship between the RT and the angular distance of the stimulus with respect to its upright orientation ($F(1.11) = 31.387$, $P < 001$), indicating that subjects actually performed a mental rotation of letters during this task. The effect of ORIENTATION was not different across TMS conditions ($F < 1$).

EXPERIMENT 2

The results of Experiment 1 suggest that both BA4 are involved in hand laterality judgments. This deficit is unlikely to result from interference with visual processing of the stimulus or allocation of attentional resources since no comparable deficit was found in a letter rotation task matched for difficulty. However, it could be argued that the recruitment of the BA4 hand motor representation during hand laterality judgments reflects a mirror mechanism involved in hand recognition and/or access to semantic knowledge such as the respective position of fingers. Previous studies have been shown that displaying an unmoving hand does not affect CS excitability, as estimated with single pulse TMS applied over BA4 [Pelgrims et al., 2005; Urgesi et al., 2006]. However, in these studies, the tasks performed by the participants did not require processing the relative finger position, which is crucial to identify hand laterality.

To ascertain that the deficit in MI found in Experiment 1 was not related to impaired perception of hand posture and/or access to the meaning of these postures, we designed a Finger Naming task that requires visual processing of hand dorsal views and access to semantic knowledge about the fingers name but, critically, this control task does not require processing the hand orientation. Therefore any deficit in this task following BA4 virtual lesions could reasonably be regarded as evidence for an involvement of BA4 in the visual/semantic processing of the hand and fingers.

Finally, because in Experiment 1 only one muscle was monitored (FCR), it is sensible to assume that the subthreshold TMS we applied over BA4 was, in some trials, suprathreshold for other arm and hand muscles, hampering our conclusions. To investigate this issue, in the present experiment EMG recordings were performed in 4 distal and proximal hand muscles in addition to the FCR.

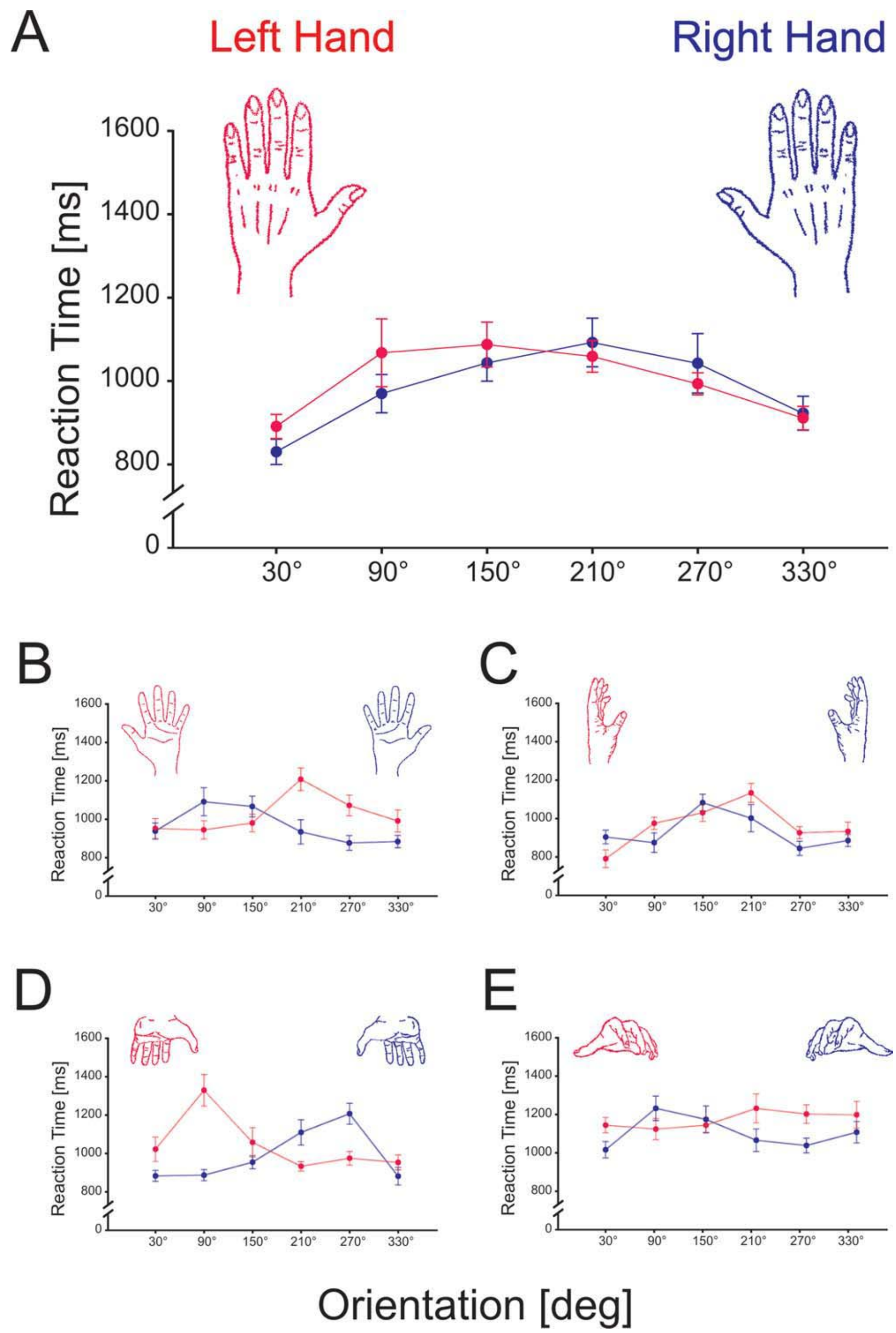

Figure 3.

MATERIALS AND METHODS

Subjects

A second group of nine right-handed volunteers (all males, age: 23 ± 3.2 years, mean ± SD) participated in Experiment 2. All the other criteria to participate in this experiment were the same as in Experiment 1.

Task Description

Stimuli were drawings of dorsal views of either a right ($n = 5$) or a left ($n = 5$) hand; for each hand stimulus, one digit was outlined in red. Subjects were required to name the red-outlined digit (see Fig. 4A). They had to provide verbally the name of the digit (i.e. "Pouce" (Thumb), "Index" (Index), "Majeur" (Middle), "Annulaire" (Ring), "Auriculaire" (Pinkie)) as quickly as possible. Stimulus display and the time course of trials were identical to those of Experiment 1. Verbal responses were noted on-line by the experimenter and analyzed off-line in order to eliminate error trials. RT was measured on-line by means of a voice key connected to E-prime.

Transcranial Magnetic Stimulation

The rTMS procedure and application were the same as in Experiment 1 except that, because this control task was easier (as evidenced by a pilot study), the duration of the train delivered at a frequency of 10 Hz was decreased from 400 (5 pulses) to 300 ms (4 pulses); as in Experiment 1, rTMS was delivered 100 ms after the onset of the stimulus display (see Fig 4A). In this experiment, the activity of the following right hand muscles was monitored in addition to the left and right FCR: First Dorsal Interosseous (FDI), Abductor Policis Brevis (APB), Abductor Minimi Digiti (AMD) and Extensor Digitorum Communis (EDC). However, as in Experiment 1, the "hot spot" and rMT for both BA4 were determined for the contralateral FCR. Finally, the vertex was used as a control site.

Experimental Design

The experiment was conducted in a single session in which three different TMS conditions were tested: (1) rTMS over the right BA4, (2) rTMS over the left BA4, and (3) rTMS applied over the vertex, used as a control site. The order of these three TMS conditions was counter-balanced across subjects. Right and left hands drawings were presented in different blocks and an equal number of stimuli with each red-outlined digit was presented. Altogether, one experiment consisted of six blocks (two hands × three TMS conditions) of 30 trials (each red-outlined digit presented six times). In each block, the stimuli were presented pseudorandomly so that the same response never occurred more than three times in a row. Before the TMS session, subjects performed 30 practice trials.

Data Analysis

The following trials were discarded from the analyses: error trials (1.8%), trials in which the verbal response was inaudible (1.4%), trials with an RT falling outside the range of the mean individual RT ± 2 SD (4.7%) and trials with an EMG activity larger than 50 μV during rTMS (17.4%). The effects of the BA4 virtual lesions were investigated on the remaining trials (75.3%), by means of an ANOVA with HAND (Right vs. Left), DIGIT (thumb,

Figure 3.

Mean RT as a function of the orientation for each hand posture (a side view, a thenar/hypothenar eminence view, a palm view, a back view and a front view of the finger tips) of the left (red) and the right (blue) hand during the MI task, computed over all TMS conditions (Experiment 1). Error bars represent the within-subject standard error of the mean [Loftus and Masson, 1994]. **A**: Back view of the hand (see Results section for more details). **B:** In the hand palm view, the RT was marginally longer when right hands were presented at 90° than 270° and 330° ($F(11.55) = 2.999$, $P < 0.018$; all Tukey t-tests, $P < 0.079$) and significantly increased when left hands were presented at 210° than 30°, 90°, 150°, and 330° ($F(11.55) = 4.307$, $P < 0.002$; all Tukey t-tests, $P < 0.029$). Accordingly, hand adduction (or ulnar inclination) can be performed over a larger angle than abduction. **C**: In the hand side view, the slowest RT were found for right hands presented at an angle of 150° when compared with stimuli rotated at 30°, 90°, 270°, 330° ($F(11.55) = 5.184$, $P < 0.001$; all Tukey t-tests, $P < 0.029$) and for left hands presented at an angle of 210° when compared with angles of 30°, 270°, and 330° ($F(11.55) = 6.655$, $P < 0.001$; all Tukey t-tests, $P < 0.049$). Accordingly, the palmar flexion of the hand can be performed over a larger amplitude than extension. **D**: In the thenar/hypothenar eminence view, the RT was longer when right hands were presented at 270° relative to 30°, 90°, 150°, and 330° angles ($F(11.55) = 9.607$, $P < 0.001$; all Tukey t-tests, $P < 0.003$) and when left hands were presented at 90° than at 30°, 210°, 270°, 330° angles ($F(11.55) = 4.354$, $P < 0.002$; all Tukey t-tests, $P < 0.047$). This result is compatible with the more limited amplitude of wrist pronation than supination when starting the movement from the canonical point of that hand posture. **E**: In the front view of the finger tips, right hand stimuli presented with an angle of 90° gave rise to a longer RT when compared with 30°, 210°, 270° angles ($F(11.55) = 4.168$, $P < 0.003$; all Tukey t-tests, $P < 0.03$). Despite a clear mirror image of the RT profile for the left hand relative to the right hand, no effect of the angular distance ($F < 1$) was observed for the left hand. This RT profile is nevertheless compatible with an awkward pronation than supination when starting the movement from the canonical point of that hand posture.

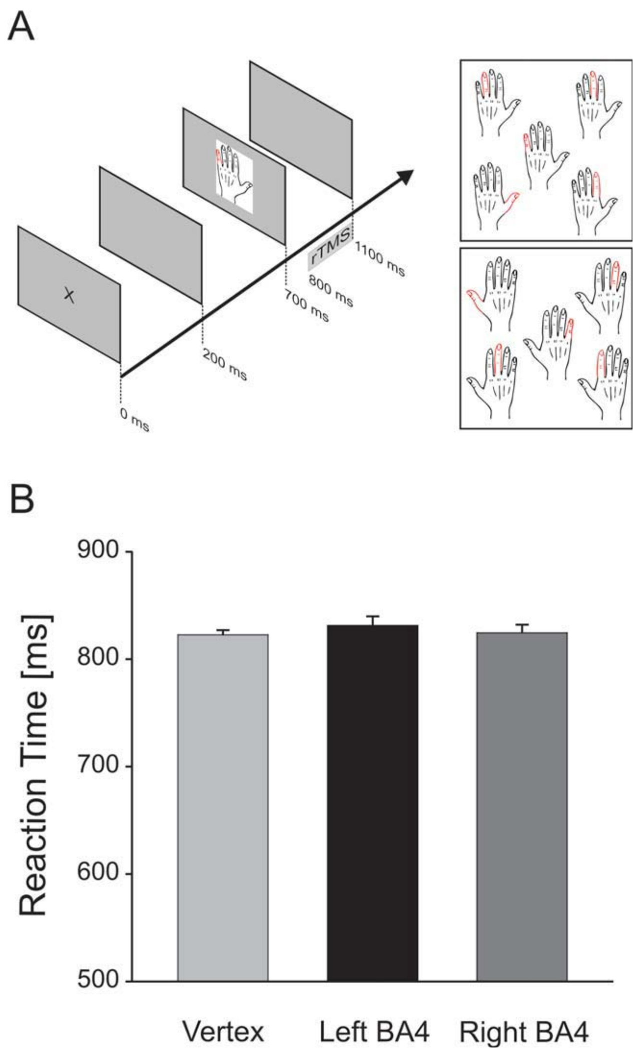

Figure 4.

A: Time course and schematic view of the Finger Naming task (Experiment 2). The insets show the left and right hand drawings used in this task. Participants had to name the red-outlined finger. **B**: Mean RT following TMS over the left and right BA4, and over the Vertex, chosen as a control site. No significant difference was observed between these TMS conditions. Error bars represent the within-subject standard error of the mean [Loftus and Masson, 1994].

index, middle, ring, pinkie) and TMS (left, right or Vertex) as within-subject factors.

Finally, the background EMG activity in the different conditions were compared by means of a supplementary ANOVA with HAND and TMS as within subject-factors, performed on the RMS of the EMG signal recorded from each muscle during a period of 200 ms before the TMS. The supplementary analyses showed that none of the aforementioned analysis factors influenced the RMS in the right or the left hand (all P-values >0.1). The mean RMS in the left and right FCR are presented in Table II as a function of each TMS condition.

When appropriate, post-hoc comparisons were performed using Tukey corrected t tests ($\alpha = 0.05$).

RESULTS

Behavioral Data

The 2 × 3 ANOVA with HAND and TMS as within-subject factors failed to reveal any effect of TMS ($F < 1$). In other words, we did not observe any RT increase when TMS was applied over the left (831 ± 158 ms) or right BA4 (824 ± 170 ms) when compared with the vertex condition (822 ± 158) (all $P > 0.1$), indicating that BA4 is not causally involved in the visual analysis of the hand and fingers and the retrieval of their name (see Fig. 4B). The main effect of HAND ($F < 1$) and the HAND by TMS (F (2.16) = 1.4, $P > 0.274$) interaction were not significant.

EMG Recordings

In order to test whether the presence or absence of an MEP in the FCR was independent of the presence or absence of an MEP in another right arm or hand muscle, we conducted a chi-square test on the trials gathered in the left BA4 condition (no MEP was observed in the right hand after TMS over the right BA4 or Vertex). Trials were classified as a function of whether TMS evoked an MEP (amplitude > 50 μV) in the FCR only, in the FCR and at least one other muscle (APB, FDI, ADM, or EDC), in at least one other muscle than the FCR, or in no muscle. This analysis revealed a high probability of observing an MEP concomitantly in the FCR and in other muscles ($\chi^2(1) = 216.9$, $P < 0.0001$). The average percentage of trials in which an MEP was elicited in a right hand muscle but not in the FCR was almost negligible, i.e. only 2.58% of the trials in the left BA4 condition. These data indicate that the results reported in Experiment 1 were not biased by the fact that subthreshold TMS elicited MEPs in other hand muscles and not in the FCR.

DISCUSSION

The aims of this study were to determine whether BA4 is causally involved in MI and if so, whether this function

TABLE II. Mean (± S.D.) RMS (μV) in the left and right FCR during the Finger Naming task, as function of TMS condition (experiment 2)

Hand	Vertex	Left TMS	Right TMS
Left FCR	0.0070 ± 0.0026	0.0059 ± 0.0015	0.0067 ± 0.0031
Right FCR	0.0141 ± 0.0041	0.0124 ± 0.0033	0.0154 ± 0.0070

is lateralized in one hemisphere. We were also interested in discriminating between different possible interpretations about the role of BA4 in MI tasks. In particular, we tested whether BA4 could be involved in the visual or semantic processing of hand postures.

In Experiment 1, we applied rTMS over either left or right BA4 to interfere transiently with its function in subjects performing a mental rotation task on hand drawings. To avoid the possible drawback of previous TMS studies [Ganis et al., 2000; Sauner et al., 2006; Tomasino et al., 2005], we used a subthreshold TMS intensity to exclude any side effect that may be caused by TMS-induced hand movements. Subthreshold intensities, combined with the use of a small figure-of-eight coil (with a 70 mm outer diameter), also allow for more focal stimulation by narrowing the magnetic field produced by the coil, thus enabling BA4 stimulation without spreading to premotor areas [Noirhomme et al., 2004]. Indeed, spatially selective deficits have been observed in studies using subthreshold rTMS applied over BA4 and the dorsal premotor cortex [Chouinard et al., 2005] or even over the representations of the lip and hand inside BA4 [Mottonen and Watkins, 2009]. In this study, the use of this optimized subthreshold rTMS protocol revealed that (1) BA4 virtual lesions selectively impaired the performance of the MI task, leaving the control letter rotation task unaffected, which therefore confirms the causal role of BA4 in MI; (2) both left and right BA4 are equally involved in MI, irrespective to the laterality (left/right) of hand drawings to be rotated.

In Experiment 2, the same interferential protocol was used to assess the potential contribution of BA4 in the recognition and access to the meaning of a hand stimulus, independently of mental rotation. This issue is particularly relevant given that numerous studies have investigated the role of BA4 in MI by using tasks based on hand drawings (e.g. [Ganis et al., 2000; Kosslyn et al., 1998; Sauner et al., 2006; Tomasino et al., 2005]. The results of Experiment 2 failed to demonstrate any TMS interference in a finger naming task, indicating that BA4 is not causally involved in the visual analysis and the access to semantic information about a hand. The deficits observed in hand laterality judgments, in Experiment 1, can therefore been interpreted as the consequences of an impairment of the central process underlying MI. Our results further suggest that the critical parameter in studies showing an increased activation in BA4 during the observation of hand movements [Caetano et al., 2007; Dushanova and Donoghue, 2010; Fadiga et al., 1995; Montagna et al., 2005; Nishitani and Hari, 2000] was the kinematic aspects, or the action concept, instead of the nature of the stimulus. This view is corroborated by previous data collected in our laboratory demonstrating that the observation of a hand picture does not increase the CS excitability more than the observation of a dimming point [Pelgrims et al., 2005].

Therefore, this study provides strong evidence for a causal role of BA4 in MI. Although some neuroimaging studies have disputed the view that BA4 is involved in MI [Gerardin et al., 2000; Stephan et al., 1995], others have provided some support for this idea by showing an increased activation in BA4 during MI [Ehrsson et al., 2003; Lacourse et al., 2005; Lotze et al., 1999; Porro et al., 1996]. The same discrepancy is also present in previous TMS studies since, in some instances, MI impairments have been reported following BA4 virtual lesions [Ganis et al., 2000; Tomasino et al., 2005] whereas some studies have failed to find any effect [Sauner et al., 2006]. Moreover, the use of suprathreshold TMS in these studies made the interpretation of these results uncertain. In the present study, we circumvented this difficulty by using a subthreshold TMS intensity determined with respect to the rMT of the contralateral FCR, a muscle whose action is essential in wrist movements. All trials in which an MEP was observed, despite this subthreshold intensity, were excluded from the analyses. Our subthreshold TMS protocol was validated by recording other extrinsic and intrinsic muscles of the right hand in Experiment 2. This control experiment showed that setting the TMS intensity at 90% of the rMT of the contralateral FCR, in Experiment 1, was adequate to make sure rTMS did not elicit MEPs in other hand muscles, whose rMT may be lower.

This study demonstrates that BA4 virtual lesions distinctively impaired the performance in a hand drawing rotation task but left unaffected a letter rotation task. Still, it could be argued that because the hand drawings and letters were, respectively, 3D and 2D stimuli, this difference may have biased our results. However, it has been shown that the mental rotation of nonmotor 3D and 2D stimuli recruits the exact same brain network, from which BA4 is excluded [Jordan et al., 2001], indicating that the absence of effect of BA4 TMS on the Letter task cannot be explained by the 2D nature of the stimuli. Therefore, it is most likely that the critical factor responsible for the dissociation found between the two tasks we investigated was the use of motor simulation of hand movements to perform the hand laterality judgment task. Consistent with previous TMS investigations [Ganis et al., 2000; Tomasino et al., 2005], we failed to find any relationship between the rotation angle of the hand drawings and the size of the effects of BA4 virtual lesions, but it remains possible that movement amplitude is coded at a single cell level which cannot be investigated by TMS [Georgopoulos et al., 1989a,b; Kakei et al., 1999].

If BA4 does indeed contribute to MI, the question arises as to why its activation does not trigger overt movements. Indeed, because of the numerous direct and indirect connections between BA4 and spinal motoneurones [Lemon et al., 2004], an increase in BA4 activity should, in theory, lead to muscle contraction. One possible explanation for this paradox is that during MI the activation of BA4 is infraliminar and therefore insufficient to trigger an overt movement. Support for this view comes from the finding that BA4 activation is much weaker during MI than during ME [Ehrsson et al., 2003; Lacourse et al., 2005; Porro et al., 1996; Sharma et al., 2008], the increase in BA4 BOLD signal during MI being only 30% of that found in ME [Porro et al., 1996; Roth et al., 1996]. The reason for such a low BA4 activation during MI could be an increase—or an absence of release—of the inhibitory drive originating from many other cortical areas that prevent motor execution. This hypothesis is corroborated by the results of two recent fMRI studies using causal connectivity analyses and showing that the interactions between the supplementary motor area, the posterior parietal lobe, the premotor cortex and BA4 are facilitatory during ME but inhibitory during MI [Kasess et al., 2008; Solodkin et al., 2004]. The existence of these inhibitory connections has been substantiated by recent TMS studies and, more precisely, it has been shown that both the ventral (F5) and dorsal (F2) premotor cortex exert at rest a net inhibitory influence on BA4 [Davare et al., 2008; Koch et al., 2006; Mochizuki et al., 2004] and the release of this inhibition seems to play a key role in calibrating overt movements [Davare et al., 2008]. Therefore, it is sensible to assume that, if these inhibitory interactions remain active during MI to prevent ME, the low BA4 activation is sometimes difficult to detect in functional imaging studies, explaining the discrepant results found in that literature [Binkofski et al., 2000; Gerardin et al., 2000; Ruby and Decety, 2001].

The second issue we wanted to investigate in the present study is the hemispheric lateralization of MI processes performed by BA4. Our results clearly indicate that both BA4 are necessary to achieve a laterality judgment on hand drawings, a unilateral lesion of BA4 being sufficient to impair the MI task. This finding is at variance with the left hemispheric dominance for MI reported in a previous TMS study [Tomasino et al., 2005]. However, because TMS was delivered at a relatively short delay with respect to the whole task duration, it is plausible that the contribution of the right BA4 remained undetected in the previous study. Actually, a slight but non-significant RT increase was observed following right BA4 TMS, leading those authors to conclude that the right BA4 hand area participates in mental rotation of hands but to a lesser degree than the left BA4 [Tomasino et al., 2005]. The present study allowed us to clarify this issue because we used rTMS to interfere with MI over a longer time period. Our results are consistent with brain imaging studies showing that both BA4 are equally involved in the handedness judgment of a given hand posture [Creem-Regehr et al., 2007; Parsons, 1998; Vingerhoets et al., 2002].

In patients with hemiparesis [Steenbergen et al., 2007] and dystonia [Fiorio et al., 2006], two pathological conditions involving BA4 in the hemisphere controlateral to the deficit, the ability to generate motor images of the affected limb is often preserved. Indeed, these patients only perform a small number of errors in a hand mental rotation task and their RT remains proportional to the angular distance of the stimulus (see also [Dominey et al., 1995; Sirigu et al., 1995]). However, in general, their RT was found increased for drawings of both the ipsilesional and contralesional hands. These observations corroborate the results of the present study, and of previous investigations in which TMS applied over the left and right BA4 led to longer RT in MI tasks, but failed to reveal a cross-lateralization for the mental rotation processes [Ganis et al., 2000; Tomasino et al., 2005].

This absence of cross-lateralization may indicate that each BA4 contributes to different aspects of the mental rotation process, irrespective of the hand laterality. As suggested for the control of reaching movements [Sainburg, 2002; Schaefer et al., 2007], the left BA4 may specify the initial direction and amplitude of the simulated movement, whereas achieving the final position of the hand accurately may require the contribution of the right BA4. Alternatively, it has been suggested that each BA4 may evaluate the compatibility, in terms of biomechanical constraints, between the mental rotation outcome and the hand it controls [Collet et al., 2000; Johnson, 2000; Papadelis et al., 2007; Parsons, 1994; Stevens, 2005]. This hypothesis does not imply a correlation between the TMS-induced deficit and the rotation angle of hand drawings because, according to this view, BA4 does not contribute to the mental rotation per se. However, our finding that unilateral TMS slows down judgments made on both left and right hand drawings questions the assumption that each BA4 provides kinesthetic feedback for the controlateral hand only. We speculate that the mental rotation outcome must be compared with both hand representations to determine the hand drawing laterality, making performance vulnerable to lesion of either region. To determine precisely the dominance of the left and right BA4 for simulating unilateral hand movements [Tessari et al., 2007; Tessari and Rumiati, 2004], future research should use MI tasks that permit testing of each hand separately [Collet et al., 2000; Johnson, 2000; Papadelis et al., 2007; Parsons, 1994; Stevens, 2005]

In conclusion, we showed that subthreshold TMS applied over BA4 disrupts mental rotation of either hand, suggesting that this region is necessary to perform MI. We argue that nonprimary motor areas exert an inhibitory influence on BA4 during MI in order to prevent overt movements, making erratic the detection of BA4 activation in fMRI studies. Whereas ME is still regarded as the principal function of BA4, the present study highlights its contribution to higher cognitive processes such as those involved in hand laterality judgment tasks. Moreover, our results discriminate for the first time between alternative interpretations regarding the role of BA4 in this task, by showing that the integrity of BA4 is a necessary condition for mental rotation (Experiment 1) but not hand recognition (Experiment 2).

ACKNOWLEDGMENTS

The authors thank Jeremy Badler for the English corrections.

REFERENCES

Binkofski F, Amunts K, Stephan KM, Posse S, Schormann T, Freund HJ, Zilles K, Seitz RJ (2000): Broca's region subserves imagery of motion: A combined cytoarchitectonic and fMRI study. Hum Brain Mapp 11:273–285.

Caetano G, Jousmaki V, Hari R (2007): Actor's and observer's primary motor cortices stabilize similarly after seen or heard motor actions. Proc Natl Acad Sci USA 104:9058–9062.

Chouinard PA, Leonard G, Paus T (2005): Role of the primary motor and dorsal premotor cortices in the anticipation of forces during object lifting. J Neurosci 25:2277–2284.

Collet C, Roure R, Dittmar A, Vernet-Maury E (2000): The activity of the vegetative nervous system like witness of themental imagery in the sportsmen, his role in the performance and the training. Sci Sports 15:261–263.

Creem-Regehr SH, Neil JA, Yeh HJ (2007): Neural correlates of two imagined egocentric transformations. Neuroimage 35: 916–927.

Davare M, Lemon R, Olivier E (2008): Selective modulation of interactions between ventral premotor cortex and primary motor cortex during precision grasping in humans. J Physiol 586(Part 11):2735–2742.

Dominey P, Decety J, Broussolle E, Chazot G, Jeannerod M (1995): Motor imagery of a lateralized sequential task is asymmetrically slowed in hemi-Parkinson's patients. Neuropsychologia 33:727–741.

Dushanova J, Donoghue J (2010): Neurons in primary motor cortex engaged during action observation. Eur J Neurosci 31:386–398.

Ehrsson HH, Geyer S, Naito E (2003): Imagery of voluntary movement of fingers, toes, and tongue activates corresponding body-part-specific motor representations. J Neurophysiol 90: 3304–3316.

Fadiga L, Buccino G, Craighero L, Fogassi L, Gallese V, Pavesi G (1999): Corticospinal excitability is specifically modulated by motor imagery: A magnetic stimulation study. Neuropsychologia 37:147–158.

Fadiga L, Craighero L, Olivier E (2005): Human motor cortex excitability during the perception of others' action. Curr Opin Neurobiol 15:213–218.

Fadiga L, Fogassi L, Pavesi G, Rizzolatti G (1995): Motor facilitation during action observation: A magnetic stimulation study. J Neurophysiol 73:2608–2611.

Fiorio M, Tinazzi M, Aglioti SM (2006): Selective impairment of hand mental rotation in patients with focal hand dystonia. Brain 129(Part 1):47–54.

Ganis G, Keenan JP, Kosslyn SM, Pascual-Leone A (2000): Transcranial magnetic stimulation of primary motor cortex affects mental rotation. Cereb Cortex 10:175–180.

Georgopoulos AP, Crutcher MD, Schwartz AB (1989a): Cognitive spatial-motor processes. III. Motor cortical prediction of movement direction during an instructed delay period. Exp Brain Res 75:183–194.

Georgopoulos AP, Lurito JT, Petrides M, Schwartz AB, Massey JT (1989b): Mental rotation of the neuronal population vector. Science 243:234–236.

Gerardin E, Sirigu A, Lehericy S, Poline JB, Gaymard B, Marsault C, Agid Y, Le Bihan D (2000): Partially overlapping neural networks for real and imagined hand movements. Cereb Cortex 10:1093–1104.

Johnson SH (2000): Thinking ahead: the case for motor imagery in prospective judgements of prehension. Cognition 74:33–70.

Jordan K, Heinze HJ, Lutz K, Kanowski M, Jancke L (2001): Cortical activations during the mental rotation of different visual objects. Neuroimage 13:143–152.

Kakei S, Hoffman DS, Strick PL (1999): Muscle and movement representations in the primary motor cortex. Science 285:2136–2139.

Kasess CH, Windischberger C, Cunnington R, Lanzenberger R, Pezawas L, Moser E (2008): The suppressive influence of SMA on M1 in motor imagery revealed by fMRI and dynamic causal modeling. Neuroimage 40:828–837.

Keel JC, Smith MJ, Wassermann EM (2001): A safety screening questionnaire for transcranial magnetic stimulation. Clin Neurophysiol 112:720.

Koch G, Franca M, Del Olmo MF, Cheeran B, Milton R, Alvarez Sauco M, Rothwell JC (2006): Time course of functional connectivity between dorsal premotor and contralateral motor cortex during movement selection. J Neurosci 26:7452–7459.

Kosslyn SM, DiGirolamo GJ, Thompson WL, Alpert NM (1998): Mental rotation of objects versus hands: Neural mechanisms revealed by positron emission tomography. Psychophysiology 35:151–161.

Lacourse MG, Orr EL, Cramer SC, Cohen MJ (2005): Brain activation during execution and motor imagery of novel and skilled sequential hand movements. Neuroimage 27:505–519.

Lemon RN, Kirkwood PA, Maier MA, Nakajima K, Nathan P (2004): Direct and indirect pathways for corticospinal control of upper limb motoneurons in the primate. Prog Brain Res 143:263–279.

Loftus GR, Masson MEJ (1994): Using confidence intervals in within-subject designs. Psychonomic Bull Rev 1:476–490.

Lotze M, Montoya P, Erb M, Hulsmann E, Flor H, Klose U, Birbaumer N, Grodd W (1999): Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. J Cogn Neurosci 11:491–501.

Maruff P, Wilson PH, De Fazio J, Cerritelli B, Hedt A, Currie J (1999): Asymmetries between dominant and non-dominant hands in real and imagined motor task performance. Neuropsychologia 37:379–384.

Mochizuki H, Huang YZ, Rothwell JC (2004): Interhemispheric interaction between human dorsal premotor and contralateral primary motor cortex. J Physiol 561(Part 1):331–338.

Montagna M, Cerri G, Borroni P, Baldissera F (2005): Excitability changes in human corticospinal projections to muscles moving hand and fingers while viewing a reaching and grasping action. Eur J Neurosci 22:1513–1520.

Mottonen R, Watkins KE (2009): Motor representations of articulators contribute to categorical perception of speech sounds. J Neurosci 29:9819–9825.

Nishitani N, Hari R (2000): Temporal dynamics of cortical representation for action. Proc Natl Acad Sci USA 97:913–918.

Noirhomme Q, Ferrant M, Vandermeeren Y, Olivier E, Macq B, Cuisenaire O (2004): Registration and real-time visualization of transcranial magnetic stimulation with 3-D MR images. IEEE Trans Biomed Eng 51:1994–2005.

Papadelis C, Kourtidou-Papadeli C, Bamidis P, Albani M (2007): Effects of imagery training on cognitive performance and use of physiological measures as an assessment tool of mental effort. Brain Cogn 64:74–85.

Parsons LM (1987a): Imagined spatial transformation of one's body. J Exp Psychol Gen 116:172–191.

Parsons LM (1987b): Imagined spatial transformations of one's hands and feet. Cognit Psychol 19:178–241.

Parsons LM (1994): Temporal and kinematic properties of motor behavior reflected in mentally simulated action. J Exp Psychol Hum Percept Perform 20:709–730.

Parsons LM (1998): The neural basis of implicit movements used in recognising hand shape. Cogn Neuropsychol 15(6/7/8): 583–615.

Parsons LM (2001): Integrating cognitive psychology, neurology and neuroimaging. Acta Psychol (Amst) 107(1-3):155–181.

Parsons LM, Fox PT, Downs JH, Glass T, Hirsch TB, Martin CC, Jerabek PA, Lancaster JL (1995): Use of implicit motor imagery for visual shape discrimination as revealed by PET. Nature 375:54–58.

Pelgrims B, Andres M, Olivier E (2005): Motor imagery while judging object-hand interactions. Neuroreport 16: 1193–1196.

Pelgrims B, Andres M, Olivier E (2009): Double dissociation between motor and visual imagery in the posterior parietal cortex. Cereb Cortex 19:2298–2307.

Petit LS, Pegna AJ, Mayer E, Hauert CA (2003): Representation of anatomical constraints in motor imagery: Mental rotation of a body segment. Brain Cogn 51:95–101.

Porro CA, Francescato MP, Cettolo V, Diamond ME, Baraldi P, Zuiani C, Bazzocchi M, di Prampero PE (1996): Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. J Neurosci 16:7688–7698.

Roth M, Decety J, Raybaudi M, Massarelli R, Delon-Martin C, Segebarth C, Morand S, Gemignani A, Decorps M, Jeannerod M (1996): Possible involvement of primary motor cortex in mentally simulated movement: A functional magnetic resonance imaging study. Neuroreport 7:1280–1284.

Rothwell JC, Hallett M, Berardelli A, Eisen A, Rossini P, Paulus W (1999): Magnetic stimulation: Motor evoked potentials. The international federation of clinical neurophysiology. Electroencephalogr Clin Neurophysiol Suppl 52:97–103.

Ruby P, Decety J (2001): Effect of subjective perspective taking during simulation of action: A PET investigation of agency. Nat Neurosci 4:546–550.

Sainburg RL (2002): Evidence for a dynamic-dominance hypothesis of handedness. Exp Brain Res 142:241–258.

Sauner D, Bestmann S, Siebner HR, Rothwell JC (2006): No evidence for a substantial involvement of primary motor hand area in handedness judgements: A transcranial magnetic stimulation study. Eur J Neurosci 23:2215–2224.

Schaefer SY, Haaland KY, Sainburg RL (2007): Ipsilesional motor deficits following stroke reflect hemispheric specializations for movement control. Brain 130(Part 8rpar;:2146–2158.

Sekiyama K (1982): Kinesthetic aspects of mental representations in the identification of left and right hands. Percept Psychophys 32:89–95.

Sharma N, Jones PS, Carpenter TA, Baron JC (2008): Mapping the involvement of BA 4a and 4p during Motor Imagery. Neuroimage 41:92–99.

Sirigu A, Cohen L, Duhamel JR, Pillon B, Dubois B, Agid Y, Pierrot-Deseilligny C (1995): Congruent unilateral impairments for real and imagined hand movements. Neuroreport 6: 997–1001.

Sirigu A, Duhamel JR (2001): Motor and visual imagery as two complementary but neurally dissociable mental processes. J Cogn Neurosci 13:910–919.

Solodkin A, Hlustik P, Chen EE, Small SL (2004): Fine modulation in network activation during motor execution and motor imagery. Cereb Cortex 14:1246–1255.

Steenbergen B, van Nimwegen M, Craje C (2007): Solving a mental rotation task in congenital hemiparesis: motor imagery versus visual imagery. Neuropsychologia 45:3324–3328.

Steenhuis RE, Bryden MP (1989): Different dimensions of hand preference that relate to skilled and unskilled activities. Cortex 25:289–304.

Stephan KM, Fink GR, Passingham RE, Silbersweig D, Ceballos-Baumann AO, Frith CD, Frackowiak RS (1995): Functional anatomy of the mental representation of upper extremity movements in healthy subjects. J Neurophysiol 73:373–386.

Stevens JA (2005): Interference effects demonstrate distinct roles for visual and motor imagery during the mental representation of human action. Cognition 95:329–350.

Stinear CM, Byblow WD, Steyvers M, Levin O, Swinnen SP (2006): Kinesthetic, but not visual, motor imagery modulates corticomotor excitability. Exp Brain Res 168(1-2):157–164.

Tessari A, Canessa N, Ukmar M, Rumiati RI (2007): Neuropsychological evidence for a strategic control of multiple routes in imitation. Brain 130(Part 4):1111–1126.

Tessari A, Rumiati RI (2004): The strategic control of multiple routes in imitation of actions. J Exp Psychol Hum Percept Perform 30:1107–1116.

Thayer ZC, Johnson BW (2006): Cerebral processes during visuomotor imagery of hands. Psychophysiology 43:401–412.

Tomasino B, Borroni P, Isaja A, Rumiati RI (2005): The role of the primary motor cortex in mental rotation: A TMS study. Cogn Neuropsychol 22(3/4):348–363.

Urgesi C, Candidi M, Fabbro F, Romani M, Aglioti SM (2006): Motor facilitation during action observation: Topographic mapping of the target muscle and influence of the onlooker's posture. Eur J Neurosci 23:2522–2530.

Vargas CD, Olivier E, Craighero L, Fadiga L, Duhamel JR, Sirigu A (2004): The influence of hand posture on corticospinal excitability during motor imagery: A transcranial magnetic stimulation study. Cereb Cortex 14:1200–1206.

Vingerhoets G, de Lange FP, Vandemaele P, Deblaere K, Achten E (2002): Motor imagery in mental rotation: An fMRI study. Neuroimage 17:1623–1633.

Wassermann EM (1998): Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol 108:1–16.

Yahagi S, Kasai T (1998): Facilitation of motor evoked potentials (MEPs) in first dorsal interosseous (FDI) muscle is dependent on different motor images. Electroencephalogr Clin Neurophysiol 109:409–417.