Cutaneous Inputs Can Activate the Ipsilateral Primary Motor Cortex During Bimanual Sensory-Driven Movements in Humans

Satoshi Shibuya1 and Yukari Ohki2

1Department of Health and Sports Science, Faculty of Education, Tokyo Gakugei University, Tokyo 184-8501; and 2Department of Integrative Physiology, Kyorin University School of Medicine, Tokyo 181-8611 Japan

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Shibuya, Satoshi and Yukari Ohki. Cutaneous inputs can activate the ipsilateral primary motor cortex during bimanual sensory-driven movements in humans. J Neurophysiol 92: 3200–3209, 2004. First published April 28, 2004; 10.1152/jn.00937.2003. Using transcranial magnetic stimulation (TMS), we examined whether sensory input from a finger affects activity of the ipsilateral primary motor cortex (M1) when human subjects hold a virtual object bimanually and whether this ipsilateral activation varies under different contexts. Subjects used both index fingers to hold two plates, which were subjected to unpredictable pulling loads from torque motors. Loads were delivered in a random sequence to either plate or concurrently to both, although the latter occurred most frequently. Finger forces vertical to the plates and surface electromyographs from the first dorsal interosseous muscles were recorded bilaterally during the task. TMS was sometimes applied over the finger area of the left M1 at variable times relative to load onset to examine cortical excitability. Strength of TMS was set around the active motor threshold of the right finger muscle while subjects waited for loading to the handheld plates. When one plate was singly loaded, the M1 contralateral to the loaded finger was activated, causing automatic force increases in the finger. In addition, the ipsilateral M1 was activated during such loading, associated with transient force increases in the contralateral nonloaded finger. Activations in the ipsilateral M1 were also observed during concurrent loading, when activations were stronger than those following single loading of the contralateral plate. Ipsilateral activations weakened when concurrent loading was less frequent. These results suggest interactions between bilateral sensorimotor cortices during bimanual coordinated movements, with strength varying by context.

INTRODUCTION

Sensorimotor control of the hand during object manipulation is characterized by feedforward, predictive control policies based on internal models that reflect both behaviors of our motor system and the relevant properties of the external object (Johansson and Cole 1994; Wing 1996; Wolpert and Flanagan 2001). Such predictions are evident, for example, when the right hand is used to open a can of drink held in the left hand. Under such situations, the left hand shows precise anticipatory modulation of grip force, based on motor commands to the right hand, preventing the object (e.g., can) from slipping (Blakemore et al. 1998; Flanagan and Wing 1993; Johansson and Westling 1984). However, the exact mechanisms underlying the representation of internal models in the brain and the construction of anticipatory modulations to motor commands remain unclear.

When we manipulate an object, we also automatically modulate grip forces to maintain grasp stability, in case the object is subjected to unpredictably imposed external forces (Cole and Abbs 1988; Johansson and Westling 1988; Johansson et al. 1992b,c; Jones and Hunter 1992). These reactive grip responses are initiated and parametrically controlled by sensory information from the digits (Häger-Ross and Johansson 1996; Johansson et al. 1992a; Macefield et al. 1996). A particular type of sensory input may thus induce stereotyped motor response under any context. However, even in such cases, human subjects still use predictions about the properties of objects to modify the reactive response and form the most appropriate response under the current context, compensating for delays in feedback effects that may threaten grasp stability. This is seen when a human holds an object in both hands, and sensory information from a digit can induce automatic grip responses not only in the ipsilateral hand but also in the contralateral one (Ohki and Johansson 1999). Gain of the reactive response in the contralateral finger shows adaptive changes depending on feedback events informing properties of objects (i.e., response appropriateness) (Ohki and Watanabe 2004), reminiscent of the adaptation observed in self-generated movements (Witney et al. 2000). Thus selection of an internal model, which modifies self-generated motor commands, most probably influences neuronal centers involved in the reactive response.

Automatic grip response is known to involve a transcortical component, which includes descending transmissions via fast corticospinal tracts (Johansson et al. 1994). The cortical networks for the component, which is set differently under different predictions, may thus plausibly cause the adaptive changes in reactive response, e.g., radiation of response to the contralateral side. This hypothesis was examined in the current study using transcranial magnetic stimulation (TMS). As reactive response is known to involve somatosensory and motor areas (Macefield and Johansson 1994), such different sets of cortical areas might also plausibly influence self-generated movements and contribute to their adaptive changes to the current object. We therefore used the task developed by Ohki et al. (2002) in which normal human subjects bimanually manipulate one virtual object (i.e., 2 objects that are loaded concurrently in most trials). During this task, TMS was applied at various timings relative to load onset to determine whether the ipsilateral primary motor cortex (M1) is activated by sensory inputs from a finger.

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Address for reprint requests and other correspondence: Y. Ohki, Dept. of Integrative Physiology, Kyorin University School of Medicine, Shinkawa, Mitaka, Tokyo 181-8611, Japan (E-mail: ohkiy@kyorin-u.ac.jp).
The consequences of a motor command should depend on the object interacted with. Indeed, different from bimanual manipulation of a single object described in the preceding text, humans can control bimanual movements quite independently when independent objects are held in each hand (Blakemore et al. 1998). If the cortical networks for the transcortical reactive responses are indeed set differently under different contexts, sensory input to the ipsilateral M1, which underlies bilateral-coordinated movements, should be attenuated during bimanual-independent movements. We therefore also examined if such variations can be observed when human subjects predict different behaviors of objects. For this purpose, we performed cortical stimulation while the same subjects were engaged in similar bimanual manipulation tasks, but now loading to a single plate occurred most frequently. In such cases, human subjects are known to prepare for manipulation of two independent objects, and the automatic reactive response is restricted in the ipsilateral hand (Ohki et al. 2002).

METHODS

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Five healthy right-handed human volunteers (2 females, 3 males) aged between 28 and 42 years provided written informed consent to participate in the study, which was approved by the local ethics committee. The apparatus and general procedures were the same as described in a previous study (Ohki and Watanabe 2004). Briefly, subjects were seated with forearms extended anteriorly and supported by a tabletop up to the palms (Fig. 1B). With palms down, subjects used the tips of both index fingers, positioned side-by-side, to restrain an instrumented manipulandum. For each digit, the manipulandum had a horizontally oriented flat grip plate covered with suede (diameter, 30 mm; center-to-center distance, 50 mm). Each plate was connected via 10-cm-long rigid beams to separate servo-regulated torque motors (SGM-A5BWG32, Yaskawa) that could generate loading forces away from the subject at the grasp plate (0–5 N, bandwidth: 0–20 Hz, noise: <0.05 N). Normal and load forces applied by the fingertips were measured perpendicular and tangential to the grip plates, respectively (Fig. 1A).

In addition, surface EMGs were recorded from the first dorsal interosseous muscles on the left and right hands (IFDI and rFDI) in a tendon-belly manner. Signals were amplified and filtered (15 Hz to 10 kHz). Subjects were blindfolded during experiments, and the apparatus provided no sound cues.

TMS

TMS was delivered using a Magstim 200 magnetic stimulator (Magstim, UK), using a figure-8 coil (8 cm ID, 11.5 cm OD). The coil was positioned flat and tangential to the scalp surface. The junction region was over the left finger area of M1 at the optimal position for evoking short-latency EMG responses in the relaxed rFDI when inducing postero-anterior current in the brain. The weight of the coil and associated cable was counterbalanced using rubber bands suspended from an overhead gantry, and the coil was secured to the head of the subject using Velcro straps. The resting motor threshold for EMG responses in relaxed FDIs ranged from 39 to 56% of maximum stimulator output in different subjects. In one of five test series, the coil was secured with the junction region positioned similarly to that described in the preceding text but to induce lateromedial current in the brain. Lateromedial stimulation can sometimes stimulate corticospinal fibers directly, whereas postero-anterior stimulation tends to activate corticospinal fibers trans-synaptically. Thus comparison of effects by both stimulations can be used to examine corticospinal excitability (Werhahn et al. 1994). During each test series, stimulation intensity was constant (31–54% of maximum stimulator output) and set to induce a motor-evoked potential (MEP) in the rFDI with peak-to-peak amplitude of ~100 μV when delivered in the preload phase (see following text). Such weak stimulation is appropriate to test cortical activation by cutaneous inputs (Ohki et al. 1994). Mean amplitude of actual MEPs in the preload phase was 145.2 ± 63.1 (SD) μV, and no significant differences in preload MEP were observed between test series.

Load trials

Load trials, configured as shown in Fig. 2, were delivered to either one of the fingers or simultaneously to both fingers. The three load conditions [single load to the left plate (or no load to the right plate), single load to the right plate, or concurrent load] occurred in pseudorandom order in all test series. Load profile was the same as that used in previous studies (Ohki and Johansson 1999; Ohki and Watanabe 2004; Ohki et al. 2002). That is, load was superimposed on a 0.2-N constant baseline load at each grip plate; this baseline load was automatically applied when the subject contacted the grip plate. Loading comprised a load phase (phase of distal load force increase) followed by a hold phase (phase of constant load), then rapid unloading. During the first 10 ms of the load phase, load increased abruptly by 0.8 N. After this “load step,” load continued to increase at a constant rate of 4 N/s for 0.5 s to the hold phase, which was maintained for 1.0 s. The load at each digit during the hold phase was thus 3 N. The high initial load force rate served to trigger a distinct normal force response, and the following load ramp increase during the load phase guaranteed substantial response amplitude (Johansson et al. 1992b; Ohki and Johansson 1999). The interval from rapid unloading to the next load phase was randomized between 2 and 3 s. All subjects participated in five test series in a balanced order with each series comprising six blocks of 50 load trials. To prevent fatigue, short rest periods were provided between blocks.

In three of the five series [i.e., linked-object (early) series, linked-object (late) series and lateromedial series], subjects experienced concurrent load to both plates most frequently and thus prepared for

![FIG. 1. Schematic illustrations of the manipulandum and experimental setup. A: schematic illustration of the manipulandum, which comprised 2 horizontally oriented flat circular grip plates, each connected to a separate servo-regulated torque motor via a stiff beam. Normal and tangential load forces to both grasp plates were measured. B: schematic illustration of the experimental setup. Subjects used both index fingers to restrain the 2 grip plates. Surface electromyograms (EMGs) were recorded from bilateral 1st dorsal interosseous muscles, while bilateral wrists were grounded. Transcranial magnetic stimulation was delivered using a figure-8 coil. The coil was secured to the subject’s head using Velcro straps (not illustrated).](http://jn.physiology.org/doi/10.1152/jn.00491.2004)
coordinated responses by bimanual fingers as if holding a single object in both hands (Ohki and Watanabe 2004; Ohki et al. 2002). That is, in a block of 50 trials, both plates were loaded simultaneously in 40 trials (80%), while the left or right plate alone was loaded in 5 trials (10%) each (trial numbers in the 6 blocks are shown in Table 1). The latter 10 trials were randomly interspersed during the last 47 trials of the block. The linked-object (early) and the lateromedial series were designed to test cortical activity during the rising phase of the

![A. No load, B. Single load, C. Concurrent load.](image)

**TABLE 1. Trial numbers in different test series**

<table>
<thead>
<tr>
<th>Test Series</th>
<th>Without TMS</th>
<th>Pre-load (150–200)</th>
<th>Dynamic Phase</th>
<th>Static Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>25</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td><strong>Linked-object (early) &amp; lateromedial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>No load</td>
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<td>6</td>
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<tr>
<td>Single</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Concurrent</td>
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<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Linked-object (late)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No load</td>
<td>6</td>
<td>0</td>
<td>6*</td>
<td>6*</td>
</tr>
<tr>
<td>Single</td>
<td>6</td>
<td>0</td>
<td>6*</td>
<td>6*</td>
</tr>
<tr>
<td>Concurrent</td>
<td>210</td>
<td>6</td>
<td>6*</td>
<td>6*</td>
</tr>
<tr>
<td><strong>Unlinked two-object</strong></td>
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<td></td>
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<td>3</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Single</td>
<td>93</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Concurrent</td>
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<td>6</td>
<td>6</td>
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<td><strong>Unlinked left-object</strong></td>
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<td>6</td>
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<tr>
<td>Single</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Concurrent</td>
<td>6</td>
<td>0</td>
<td>6</td>
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</tr>
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</table>

The load condition at right finger is presented for all test series. In linked-object (late) series, load force-TMS probe intervals during the dynamic phase were 75, 145, and 215 ms after load onset instead of 25, 45, and 65 ms (*). TMS, transcranial magnetic stimulation.
reactive response. That is, for each loading condition in each block, TMS shock was delivered during the dynamic phase of the response in three trials and during the static phase in one trial; i.e., 25, 45 and 65, and 1,205 ms after onset of load force increase, respectively. In addition, TMS was delivered 150–200 ms before the concurrent load (preload phase) for one trial in each block. Trials with TMS probe were intermixed with control trials without TMS, and trials with different load force-TMS probe intervals were tested in a random sequence. The lateromedial series differed from the linked-object (early) series only by the direction of the induced current. Only in the lateromedial series was the current directed lateromedially in the brain, while it was directed postero-anteriorly in all other test series. In the linked-object (late) series, the latter part of the dynamic phase was examined separately to prevent subject fatigue. In this series, trial numbers and TMS intervals were as described in the preceding text, except for intervals during the dynamic phase; these were 75, 145, and 215 ms after load onset, instead of 25, 45, and 65 ms as in the other test series (cf. Table 1).

In the other two series (unlinked 2-object series and unlinked left-object series), subjects experienced isolated load to a single plate in most trials (Table 1) and thus prepared for isolated response by a single finger. In such test series, interactions between bimanual responses are known to be reduced (Ohki et al. 2002). In a block of the unlinked two-object series, the left or right plate was loaded in 20 trials (40%) each in random order, while 10 trials (20%) with concurrent loading were randomly interspersed during the last 47 trials of the block. Similarly, in a block of the unlinked left-object series, the left plate was loaded in isolation in 40 trials (80%), while single load to the right or concurrent loading occurred randomly in 5 trials (10%) each during the last 47 trials of the block. TMS probe intervals were as described for the linked-object (early) series, although TMS during the preload phase occurred in trials with the predominant loading conditions (see Table 1).

Subjects let the apparatus slip in some trials with or without TMS. In such cases, the trial was repeated after at least three additional control trials (with predominant load condition, without TMS). Such slips occurred in ~0.15% of trials in four subjects. In the other subject, slips occurred at a relatively high frequency (1.5%). However, his performance did not otherwise differ from those of the other subjects, and data from the five subjects were analyzed together. No significant differences were noted between test series with regard to frequency of slippage.

Data collection and analysis

Data were collected and analyzed using a laboratory computer system (SC/ZOOM; Physiology Section, IMB, University of Umeå). Force signals were sampled at 400 Hz. Force rates were obtained as a function of time using symmetrical numerical time differentiation within a time window corresponding to ±5 data samples off-line. EMG signals were sampled at 1,500 Hz. Rectified EMGs were obtained by taking absolute values of the EMGs off-line, which were then low-pass filtered by performing triangular moving average (±10 data samples), with a cut-off frequency (~6 dB) of 60 Hz. Event markers related to timing of TMS were also sampled (±0.1-ms resolution).

The following measurements were taken from single trials and from each digit: preload normal force was the normal force present at the onset of the load increase. Grip response onset latency was the time interval from onset of load force increase to onset of reactive normal force increase as assessed from force rate signals. One or more peaks in the normal force rate profile were identified (Fig. 2) (cf. Johansson et al. 1992b; Ohki and Johansson 1999). For the first peak, amplitude and time of occurrence was measured relative to onset of load force increase. A normal force response was considered present for maximum normal force rate >2.5 N/s: responses of weaker strengths could not be reliably detected in single trial records. In cases of weaker

forces, none of the preceding response parameters was measured, but peak rates were scaled as zero in statistical analyses. Such cases occurred only for a nonloaded finger while the contralateral finger was loaded in isolation. For the right finger, occurrence frequencies were 0% (2 linked-object and lateromedial series), 7.7% (unlinked 2-object series) and 22.2% (unlinked left-object series) in the trials. Static normal force response was measured as the difference between normal force at 100 ms before end of the hold phase and the preload normal force.

As we used weak TMS, which sometimes evoked little MEP in a single trace, MEP amplitude was measured in an averaged EMG trace, as peak-to-peak amplitude during 20–35 ms after TMS. Background EMG during the MEP was measured in an averaged rectified EMG trace, which was obtained from control trials without TMS. For each load condition and each TMS interval, background EMG was measured as the mean amplitude during 20–35 ms after TMS onset. Peak:background ratios were computed from these two values and were normalized by the corresponding values during the preload phase in the same test series.

Statistical methods

Numerical values of normal forces and EMGs were transferred to statistical software (STATISTICA, Statsoft, Tulsa OK). Unless otherwise stated, statistical reports were derived from repeated-measures ANOVA. Usually, data from loaded fingers were tested together for two load conditions [load condition (2): single or concurrent load] and those when the finger was not loaded were tested separately.

One type of ANOVA was performed to analyze variation of the peak:background ratio depending on TMS timing relative to load onset. Thus factors comprised: load condition (2) × TMS timing, when the finger was loaded; and TMS timing when the finger was not loaded. Number of levels for TMS timing was 5 when data from one test series were analyzed [TMS timing (5): preload, 3 timings in dynamic phase, and static phase] and 9 when data from two linked-object series were analyzed together [TMS timing (9): preload, 6 timings in dynamic phases, and 2 levels in static phase from 2 series]. The other type of ANOVA was performed to check difference among test series. Factors comprised: test series [3: linked-object (early) series; unlinked 2-object series; and unlinked left-object series] × load condition (2) × TMS timing (5) when the finger was loaded; and test series (3) × TMS timing (5) when the finger was not loaded.

In addition, a priori (planned) and post hoc comparisons (LSD test) were performed to analyze specific effects as described in RESULTS. The level of probability selected for statistical significance was P < 0.05, and population estimates are given in the text in the form of subject means ± SD (n = 5). For each subject and for each of the experimental conditions, values for all trials were averaged and subject mean (n = 5) was calculated for these “average trials.” Average trials were also used in statistical analyses. One SE is indicated in graphs (n = 5).

RESULTS

Normal force responses

Figure 2 (A–C) shows averaged responses of the right finger from all five subjects. Responses are from control trials without TMS in the linked-object (early) series in which concurrent load to the two plates occurred most frequently. Loading to the grip plate reliably triggered normal force responses at the loaded finger during both concurrent (Fig. 2C) and single (B) load to support grasp stability. In addition during the concurrent load, normal forces developed more rapidly than during single load, which was represented in the first force rate peak [F(1,4) = 22.1 P < 0.01; main effect by load condition (2);
leftmost white and gray columns, Fig. 2A] (cf. Ohki and Johansson 1999). Furthermore, the finger that was not loaded sometimes displayed transient force increases when the partner finger was loaded in isolation (Fig. 2A, white arrow) (cf. Ohki and Johansson 1999). In control trials of the linked-object series, mean response onset latency of the right finger was 70.3 ± 5.0 ms during concurrent loading, differing little from mean response onset latency when the finger was loaded in isolation (70.7 ± 4.9 ms; leftmost white and gray columns, Fig. 2D). As reported previously, however, latency of the right finger was significantly longer (85.0 ± 4.9 ms) when single load of the left finger induced responses from the right finger \[F(1,4) = 18.8, P < 0.05;\] planned comparison between 2 loaded conditions and no load, for a factor: load condition (3); leftmost black column in Fig. 2D).

Figure 2 (A–C) also shows rectified EMG activities of the rFDI during responses. In the preload phase, the rFDI kept active to produce holding force from the right finger during the intertrial interval. Normal force increase to the applied load was associated with complex EMG activation. During the dynamic phase, the EMG signal from rFDI corresponded well to the normal force rate signal of the right finger, both when the finger was loaded and not loaded. Interestingly, during the dynamic phase of the response, oscillatory activity changes in the EMG were observed at loaded fingers, corresponding to multiple peaks in the force rate of the same finger (Fig. 2, B and C) (cf. Johansson et al. 1992b; Ohki and Johansson 1999). On the other hand, corresponding to the static normal force increase, static increase in EMG activity occurred during the static phase at a loaded finger although the increase in EMG activity was usually smaller than the maximum EMG increase during the dynamic phase. Onset latency of response-associated activation in rFDI was 57.1 ± 3.5, 58.6 ± 7.4, and 72.9 ± 7.1 ms when the right finger was loaded concurrently, loaded in isolation, and not loaded, respectively. EMG activity thus occurred 12–13 ms earlier than the normal force increase.

Normal force responses at loaded and nonloaded fingers were observed in all subjects and in all test series. However, transient force increases at a nonloaded finger are known to change size according to subject predictions of object behavior (cf. Ohki et al. 2002). Figure 2 (D–F) shows changes in normal force responses according to behavior of the object with measurements from control trials without TMS shown. During the two unrelated-object series (unlinked 2-object and unlinked left-object series), the first force rate peak at a nonloaded finger was significantly smaller than that during linked-object series \[F(1,4) = 18.9, P < 0.05;\] planned comparison between linked-object (early) and 2 unrelated-object series (cf. Ohki et al. 2002). Corresponding changes were also observed in EMG activity increase from preload values during the dynamic phase (Fig. 2F). However, preload force did not show significant changes between linked-object (early) (2.8 ± 0.9 N), unlinked two-object (2.7 ± 0.5 N), and unlinked left-object (3.4 ± 1.2 N) series. In addition, changes due to object behavior were absent from static response irrespective of whether fingers were loaded or not.

**Cortical activity changes during linked-object series**

To test excitability changes in M1 during the linked-object series, TMS was delivered to the hand area of the left M1 at various times during tasks, during the preload phase, and at different intervals after onset of load increase (stimulus timing is shown in Fig. 2, A–C, bottom). Evoked MEPs in rFDI are indicated in Fig. 5, where mean onset latency was 21.5 ± 1.0 ms.

Figure 3 shows composite results from the early and late linked-object series. As for responses when right fingers were loaded, size of the short-latency MEPs varied substantially depending on timing of TMS delivery. This is illustrated in Fig. 3 (B and C), which shows mean amplitudes of MEPs (circles) elicited by the various TSM probes in all subjects (see also Fig.
5). In the figure, amplitudes are represented on the time scale as mean time of the occurrence of the first amplitude peak in MEP rather than by the point in time of the corresponding TMS probe. Mean latencies of the first and the second amplitude peaks in MEP were 24.6 ± 1.2 and 28.6 ± 1.8 ms, respectively (pooled data from all test series). The short latencies suggest that the fast corticospinal pathways mediated both amplitude peaks (cf. Rothwell et al. 1991). However, because background EMG also changed, this variation in MEP amplitude might simply reflect changes in motoneuronal excitability rather than in cortical excitability. To exclude effects due to background EMG changes, we normalized MEP peaks to background EMG activity by computing peak:background ratios (see METHODS). When the right finger was loaded, significant increases in the ratio were observed during normal force response \( F(8,32) = 3.3, P < 0.01; \) main effect by TMS timing, for factors: load condition \((2) \times \) TMS timing \((9); 2\) gray lines, Fig. 4A). Post hoc comparisons revealed that ratios with the 45, 65, and 75 ms probes were significantly larger than that during the preload phase \( (P < 0.05, P < 0.01, \) and \(P < 0.01, \) respectively: LSD test), but this significant increase was not observed with later probes \((145 \) and 215 ms and static phase). Similar variations in the ratio were observed during both single and concurrent loading, except that with the 45-ms probe. The ratio with the 45-ms probe did not show any significant increase during single loading, although significant increases from preload values were observed during concurrent loading \((P < 0.01; \) LSD test).

Variation of peak:background ratio during the lateromedial series was also examined. In accordance with differential activation sites between postero-anterior and lateromedial electrical currents (cf. Werhahn et al. 1994), latencies of MEPs in the lateromedial series were slightly shorter \((19.7 \pm 1.5 \) ms) than the corresponding values described in the preceding text. However, for responses of loaded right fingers, increases from preload values were observed with 65 ms \((P < 0.05; \) LSD test).

When left fingers were loaded in isolation, nonloaded right fingers displayed coupled responses with transient normal force increases as described in the preceding text. During these responses, TMS was delivered to the left M1 and peak:background ratios were obtained from MEP amplitudes to exclude effects due to background EMG changes. Peak:background ratios for the finger showed significant variation during the coupled response \( F(8,32) = 2.6, P < 0.05; \) main effect by TMS timing \((9); \) Fig. 4A, \( \cdots \cdots \), with significant increases for 65-, 75- and 145-ms probes \((P < 0.05; \) LSD test). Note that during the coupled response, activity in the rFDI was almost at the same level as that during the static phase in a loaded finger (see rectified EMG, Fig. 2, \( A\cdots C \)). However, the ratio was higher during the coupled response. Moreover, an increase in ratio was not observed for the 65-ms probe during the lateromedial series (Fig. 4B, \( \cdots \cdots \)).

MEPs induce small contractions in FDI and other hand muscles. As might be expected, these were observed as twitch-like normal force changes superimposed on the time-varying normal force response (Fig. 5, onsets marked as black triangle). By observing dependence of the twitch-like normal force changes on timing of TMS delivery, we examined total excitability changes of cortical neurons that transmitted motor commands to index finger muscles including the FDI that worked as synergies to produce normal forces. Latency of twitch-like normal force increase was 29.8 ± 2.9 ms. However, this early force increase was usually followed by a more prominent force increase (white triangle). Twitch-like and subsequent increases were sometimes continuous and difficult to distinguish. Size of twitch-like increases was quantified by measuring force increase 50 ms after TMS, which was after the start of the twitch-like increase and before the later increase. As might be expected, amplitude was highly variable during load trials in the two linked-object series \( F(4,16) > 4.7, P < 0.05 \) for both linked-object series; main effect by TMS timing when factors were load condition \((3) \times \) TMS timing \((5)\), varying in a manner similar to that of the amplitude of the TMS response peak. Comparisons with force increase during the preload phase revealed that force increase was significantly larger with 65- and 75-ms probes for all loading conditions \((P < 0.05; \) LSD test) and with the 45-ms probe only during concurrent loading \((P < 0.05; \) LSD test). Again, twitch-like force increases during the static phase were as low as preload values when the right finger was loaded and were almost absent when the finger was not loaded.

Cortical activity changes during unlinked-object test series

In the preceding section, we observed activity changes of the left M1 by sensory inputs from the left finger. However, coupled responses from nonloaded fingers are known to change size according to subject predictions of object behavior (Ohki et al. 2002). We therefore analyzed if cortical activity change can be modified by object behavior.

In accordance with the dynamic response change of the nonloaded finger (Fig. 2E, black columns), MEP with 65-ms probe was facilitated less during the unlinked two-object series than during the linked-object series and facilitated least during the unlinked left-object series (Fig. 6, A and D). Peak:back-

![FIG. 4. Peak:background ratios in different test series. Graphs are from 2 linked-object series (A), lateromedial series (B), unlinked 2-object series (C), and unlinked left-object series (D). In A, values from early and late linked-object series are shown (○ and ●, respectively). Data from different load conditions are shown separately: right fingers not loaded (●-●); loaded in isolation (●-●); and loaded concurrently with left fingers (—-). Ratios are given as percentages of preload values.](https://jn.physiology.org/)

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ground ratio also displayed this tendency (Fig. 4, C and D), and no main effect from TMS timing was observed during the unlinked-object series \[ F(4,16) / H11021 = 1.5, P / H11022 = 0.1 \] for both test series, when factor was TMS timing (5). MEP changes by test series could also be observed for responses when the finger was loaded (Fig. 6, B–C and E–F) and were reflected again in peak:background ratio (Fig. 4, C and D). Although main effects were observed by TMS timing on peak:background ratio in both unlinked-object series \[ F(4,16) / H11022 = 3.9, P / H11021 = 0.05 \]; factors were load condition (2) / H11003 TMS timing (5), significant increases in ratio were observed only with 65-ms probes for both test series (\( P / H11021 = 0.01 \); LSD test). With the 65-ms probe, similar increases were observed during both concurrent and single loading (\( P / H11021 = 0.01 \) for both load conditions in the 2 test series; LSD test).

DISCUSSION

In the present study, we used TMS to examine cortical excitability changes induced by loading to handheld objects during bimanual manipulation. The sites of activation with transcranial magnetic and anodal electrical stimulation are known to differ; anodal stimulation activates the axons of pyramidal cells in the white matter, whereas TMS activates the cells \textit{trans}-synaptically (Amassian et al. 1990; Day et al. 1989) or at the initial segments (Amassian et al. 1990; Edgley et al. 1990). This difference between the two methods of stimulation suggests that MEPs caused by TMS are more susceptible to the level of motor cortical excitability than MEPs caused by electrical stimulation, and has been used to show activity changes in M1; e.g., in studies of long-latency reflex on stretch (Day et al. 1991) and cutaneous stimulation (Ohki et al. 1994), cerebellar stimulation (Ugawa et al. 1991), and inter-hemispheric interactions of the motor cortex (Ferbert et al. 1992). The present study observed marked modulation in relative amplitude of the MEP of a finger muscle to TMS delivered to the hand area of M1 at various time points during the load trial. As noted in a previous study, modulation was observed in the M1 contralateral to the loaded finger (Johansson et al. 1994). Furthermore, we observed similar modulation in the ipsilateral M1 related to load-induced motor response in the present study. Ipsilateral modulation was clearly observed by single loading to a finger and when the contralateral nonloaded finger displayed a transient-coupled response. Moreover, during concurrent loading of the two fingers, early modulation in M1 was markedly stronger than when the contralateral finger was loaded in isolation.

As reported by Johansson, Lemon and Westling (1994), clear dissociations were observed between time courses of changes in background EMG and MEP amplitude, which was reflected in modulation of peak:background ratio (Fig. 4). If MEP amplitude changes simply reflected changes in background motoneuronal excitability and were proportional to background motoneuronal excitability, \\( P / H11021 = 0.01 \) for both load conditions in the 2 test series; LSD test). However, the response modulation actually obtained was larger than could be explained by such a proportional relationship. Nonlinear augmentation in MEP amplitude under high background activities cannot be entirely excluded. However, as described in RESULTS, dissociations in MEP amplitudes remain even when comparing MEP amplitudes under the same background EMG level (coupled response of a nonloaded finger vs. static phase of a loaded finger). We therefore infer an additional contribution to modulation of the MEP due to changes in the corticospinal volley elicited by TMS. These changes most likely reflect variations in the excitability of cortical neurons during the course of the load trial because such excitability is better probed using low-intensity TMS as used in the present study (cf. Ohki et al. 1994). Variations during load trials were also observed in

![Fig. 5. Ensemble averages across all subjects and all trials showing effects of TMS on task performance during the linked-object (early) series.](http://jn.physiology.org/)

**Fig. 5.** Ensemble averages across all subjects and all trials showing effects of TMS on task performance during the linked-object (early) series. In each panel, the top left trace shows an averaged MEP, which was induced by TMS (timing indicated by arrow). Curves with dark gray shading show a comparison of normal force responses in trials with TMS and in control trials without TMS; the difference is marked by the shaded zone. This difference was extracted by subtracting control normal force from the normal force of TMS trials and represented by light gray shading. For TMS during the preload phase, only this difference is presented. Black triangle, onset of twitch-like normal force change induced by the MEP; white triangle, start of late force increase, if present. Vertical dotted lines, timing of load onset.
twitch-like normal force changes induced by TMS, suggesting that excitability changes took place simultaneously in corticospinal neurons transmitting output to index finger muscles, which worked as synergies to produce normal forces during the current task.

To exclude modulation due to background motoneuronal excitability, we also compared two types of MEPs that were evoked by postero-anterior and lateromedial current in M1 caused by TMS. Differences in activation sites by TMS and anodal electrical stimulation are known to be clear only for small responses and for MEPs to magnetic stimulation inducing postero-anterior current (Amassian et al. 1989). Indeed, Werhahn et al. reported that lateromedial current by TMS can sometimes stimulate corticospinal fibers directly, i.e., at or near the same site as anodal electrical stimulation, and observed that responses evoked by lateromedial current were less affected by changes in motor cortical excitability than responses evoked by postero-anterior current (Werhahn et al. 1994). We therefore also compared MEPs induced by postero-anterior and lateromedial current to show excitability changes in M1 during reactive finger response. As seen in previous results, latencies of MEPs in the lateromedial series were slightly shorter than those induced by postero-anterior current. During the coupled response of a nonloaded finger, MEP amplitudes by lateromedial current changed in proportion to background EMG activities, and peak:background ratio in the lateromedial series was therefore virtually constant. Moreover, early facilitation by concurrent loading of the left finger was only observed when current was applied postero-anteriorly. We therefore concluded that loading the left finger resulted in activation in the ipsilateral left M1, causing a transient-coupled response at a nonloaded finger or response facilitation during concurrent loading. Later TMS probes displayed no dissociation in peak:background ratio of a loaded finger between the two directions of current. Indeed, values with the 65-ms probe showed clear facilitation under both current directions. This facilitation might be explained by strong excitation in the contralateral M1 during the early dynamic part of the reactive response (Johansson et al. 1994). As differences in stimulated sites under the two current conditions were relative rather than absolute, the lateromedial current could also induce trans-synaptic input to some extent, which might be facilitated by strong excitation in M1.

As described in the preceding text, activations in the ipsilateral M1 were observed both during single and concurrent loads in which coupled responses in a nonloaded finger and response facilitation in a loaded finger were observed, respectively. However, onset latency of the ipsilateral excitation differed slightly when comparing the two load conditions. That is, stronger excitation during concurrent loading compared with isolated loading was clear at the 45-ms probe, whereas the earliest excitation during transient coupled response was detected at the 65-ms probe. Earlier onset during concurrent loading could be explained by the spatial facilitation induced by concurrent contralateral input. With this mechanism, the 45-ms probe, for which the MEP appeared around the onset of
coupled response, could detect the very onset of ipsilateral excitation. However, cortical excitation cannot be detected by the 25-ms probe even during concurrent loading, although the second peak of MEP by the probe (25 ms for TMS timing + 28.6 ms for second peak latency) appeared around the onset of activity increase in background EMG (57.1 ms; see also Fig. 5). Thus as proposed in a previous study, subcortical mechanisms should have been responsible for the earliest part of the reactive response to the imposed load (Johansson et al. 1994), and ipsilateral excitation also lagged behind the reactive response onset. Also in accordance with the previous study (Johansson et al. 1994), peak:background ratio during the static phase did not differ significantly from that observed during the preload phase under any load condition despite the fact that constant EMG activities were observed during the static phase when the finger was loaded. This also agrees with earlier observations showing that corticospinal neurons are particularly active just before and during the grip phase of a task rather than during the static phase (Maier et al. 1993; Muir and Lemon 1983).

A previous study showed that size of the coupled response in a nonloaded finger varied under different contexts; i.e., with subject predictions about object behavior (Ohki et al. 2002). In the present study, variations in response were also observed when predominant load conditions differed. Moreover, corresponding to variations in response, the excitability in the ipsilateral M1 during single loading of a finger (i.e., during the coupled response in the contralateral finger) was also lower when subjects predicted single loading of either finger (unlinked 2-object) rather than concurrent loading (linked-object) and lowest when the prediction was single loading of the loaded finger (unlinked left-object). Similarly, MEP facilitation during concurrent loading was observed little during the two unlinked-object series in which single loading predominated. We thus concluded that ipsilateral excitation induced by loading of a finger could vary with subject predictions about object behavior.

The present results clearly show that the ipsilateral M1 is activated by loading a finger during bimanual manipulation tasks. Some cells in M1 are known to receive sensory input from the ipsilateral hand (Aizawa et al. 1990; Lemon and Porter 1976). The present study reveals that such ipsilateral inputs can function under certain contexts and suggests that input strength varies with context. Based on our previous observations, the gain of the ipsilateral input would be modified by experience of feedback events or by subject speculations about current contexts (Ohki and Watanabe 2004). Electrophysiological and functional-imaging studies in humans do indeed suggest the involvement of the ipsilateral hemisphere in hand movements with regard to somatosensory processing (Ledberg et al. 1995; Schnitzler et al. 1995; Yoshii et al. 1989). The anatomical pathway of the ipsilateral input during the reactive response is not yet known. However, the long-latency (so-called “long-loop”) reflex to muscle stretch or electrical stimulation of digital nerves is known to involve both somatosensory (Abbruzzese et al. 1985; Conrad et al. 1984; Crawford et al. 1986; Goodin et al. 1990) and motor cortices (Deuschl and Lucking 1990; Jenner and Stephens 1982; Matthews 1991; Palmer and Ashby 1992). Also, for generation of automatic reactive responses induced by pulling loads of a handheld manipulandum as used in the current study, cortical sensorimotor hand areas are suggested to be involved (Matsen et al. 1991). Sensory information from a finger may thus also be transmitted to ipsilateral sensorimotor areas when it is processed in the corresponding contralateral sites to induce reactive responses. Indeed, interhemispheric excitatory connections are known to exist between bilateral hand areas in M1 (Ferbert et al. 1992; Hanajima et al. 2001; Ugawa et al. 1993), although interhemispheric inhibition prevails over excitation when a unilateral M1 is stimulated with TMS. Furthermore, transcallosal pathways connecting the postcentral somatosensory cortices (Iwamura et al. 1994) could contribute to ipsilateral excitation after loading a finger. Whether the strength of bilateral functional connections in these areas varies under different contexts should be explored in future work.

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