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SHORT COMMUNICATION
High-frequency repetitive transcranial magnetic stimulation over the hand area of the primary motor cortex disturbs predictive grip force scaling

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Abstract
When we repetitively lift an object, our grip force is influenced by the mechanical object properties of the preceding lift, irrespective of whether the subsequent lift is performed with the same hand or the hand opposite to the preceding lift. This study investigates if repetitive high-frequency transcranial magnetic stimulation (rTMS) over the dominant primary motor cortex affects this relationship. After completion of 10 lifts of an object using the dominant hand, rTMS was applied over the dominant primary motor cortex for 20 s. On the first lift following rTMS, the peak grip force was significantly higher than on the lift preceding rTMS. Moreover, this measure remained elevated throughout the following set of lifts after rTMS. rTMS did not change the peak lift force generated by more proximal arm muscles. The same effect was observed when the lifts following rTMS over the dominant motor cortex were performed with the ipsilateral hand. These effects were not observed when subjects rested both hands on their lap or when a sham stimulation was applied for the same period of time. These preliminary data suggest that rTMS over the sensorimotor cortex disturbs predictive grip force planning.

Introduction
When lifting an object between the thumb and index finger, we must exert sufficient grip force to stabilize the object against the load caused by the effects of gravity. It has been demonstrated that the rate of grip force development and the balance between peak grip and load forces is programmed to match precisely the physical object properties, such as weight and surface friction (Flanagan & Johansson, 2002). The appropriate rate of grip force output is generated well before lift-off until somatosensory feedback from the grasping fingers becomes available. Unfamiliar objects require only one–three lifts to establish efficient force scaling, and during repetitive object lifting random changes in weight cause us to scale our grip force according to the previous lift (Johansson & Westling, 1988; Flanagan & Johansson, 2002). Thus, grip force is specified in a predictive manner to match precisely the load when lifting a familiar object. Importantly, these memory links transfer across hands (Gordon *et al*., 1994).

Predictive grip force scaling has been interpreted to reflect internal models (Wolpert & Flanagan, 2001). Such models allow us to predict the consequences of our own motor actions by relating the motor commands to their actual outcomes. This type of force control is based on the comparison of actual sensory signals and the predicted sensory input, an internal sensory signal referred to as *corollary discharge*. The predicted sensory input is produced by an internal forward model in conjunction with a copy of the descending motor command. A mismatch between the predicted and the actual sensory input triggers force corrections and updates the relevant internal models. The question of where to localize such internal models anatomically within the CNS is still unanswered.

Repetitive transcranial magnetic stimulation (rTMS) can be used to disrupt cortical activity and thus interferes with the normal pattern of neuronal activity during perception and motor execution (Siebner & Rothwell, 2003). The capacity of rTMS to interfere with neural activity temporarily beyond the duration of stimulation provides a tool to explore the role of distinct cortical areas in predictive force control. We report preliminary data from experiments designed to study the effects of rTMS over the hand area of the dominant primary motor cortex (M1) on the grip force subsequently used to lift a known object.

Materials and methods
Subjects
Twelve healthy subjects (four females; 22–38 years old, mean age: 29 ± 5 years) participated in the experiments. Subjects had no history of previous upper-limb injury. All subjects had a right hand preference as determined by a handedness questionnaire (Crovitz & Zener, 1965) and were completely naive to the specific purpose of the experiments. The methodology was approved by the local ethics committee. Informed consent was obtained from all participants.

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Instrumented object

The instrumented object that subjects lifted has been described previously (Nowak & Hermsdörfer, 2005). The object was mounted on top of an opaque plastic box (Fig. 1A). The mass of the object mounted on the box was 0.45 kg. Grip surfaces were covered with a medium-grain sandpaper (no. 240). The object incorporated a force sensor for grip force registration and linear acceleration sensors to register accelerations in three dimensions (see Fig. 1A). Recorded grip force and acceleration data were A-to-D converted and stored within the object. Data were transferred to a personal computer for analysis following each experimental setting.

rTMS

Focal TMS with a figure-of-eight-coil (Magstim Company, Dyfed, UK; diameter of each coil was 7 cm) was used to elicit motor-evoked potentials (MEPs) in the first dorsal interosseous muscle of the relaxed right hand. The coil was kept tangentially to the head. The short axis of the TMS coil was orientated approximately perpendicular to the central sulcus of the dominant left sensorimotor cortex with the handle pointing posteriorly. MEPs were recorded with surface electrodes. First, the optimal spot on the skull was determined as the cortical site where muscle responses were evoked at a minimum stimulator output intensity. This position was marked with ink to allow exact re-positioning of the coil throughout the experiments. After the optimal spot was localized, subjects were asked to produce a tonic pinch between the index finger and thumb at about 20% of maximal voluntary contraction. The active motor threshold was defined as the stimulator intensity that evoked five or more muscle responses out of 10 consecutive single TMS pulses.

During the rTMS condition, stimulation was applied using a recently developed protocol in which rTMS was delivered in bursts of three pulses at 50 Hz (Huang *et al*., 2005). The protocol appears to be safe; however, physiological safety issues have to be evaluated in future work (Paulus, 2005). The bursts were delivered continuously at a rate of 5 Hz (200 ms gap between each burst) at 80% active motor threshold over 20 s.

Experimental procedure

Subjects washed their hands with soap and water. They were seated in front of a table. The object was placed on the table so that reaching for it required only minimal shoulder movements. Subjects grasped the object between the thumb and index finger. The object was lifted using primarily elbow flexion. Subjects lifted the object 1 cm above the table (indicated by a marker), held it stationary for $\sim$5 s, and then replaced it. The time for each experiment was $\sim$30 min. At the end of each experiment, subjects were asked to lift the object and slowly separate the fingers until it dropped. This procedure was carried out for both hands to obtain an estimate of the minimal grip force necessary to prevent the object slipping. The slip point was defined as the first detectable change in acceleration, and the minimum grip force was determined at this time point.

Experiment 1: effects of rTMS on grip force scaling at the dominant hand

The first experiment consisted of three parts and compared the grip forces when lifting the object prior to and following 20-s periods of: (i) rTMS; (ii) sham stimulation; and (iii) motor rest. During sham

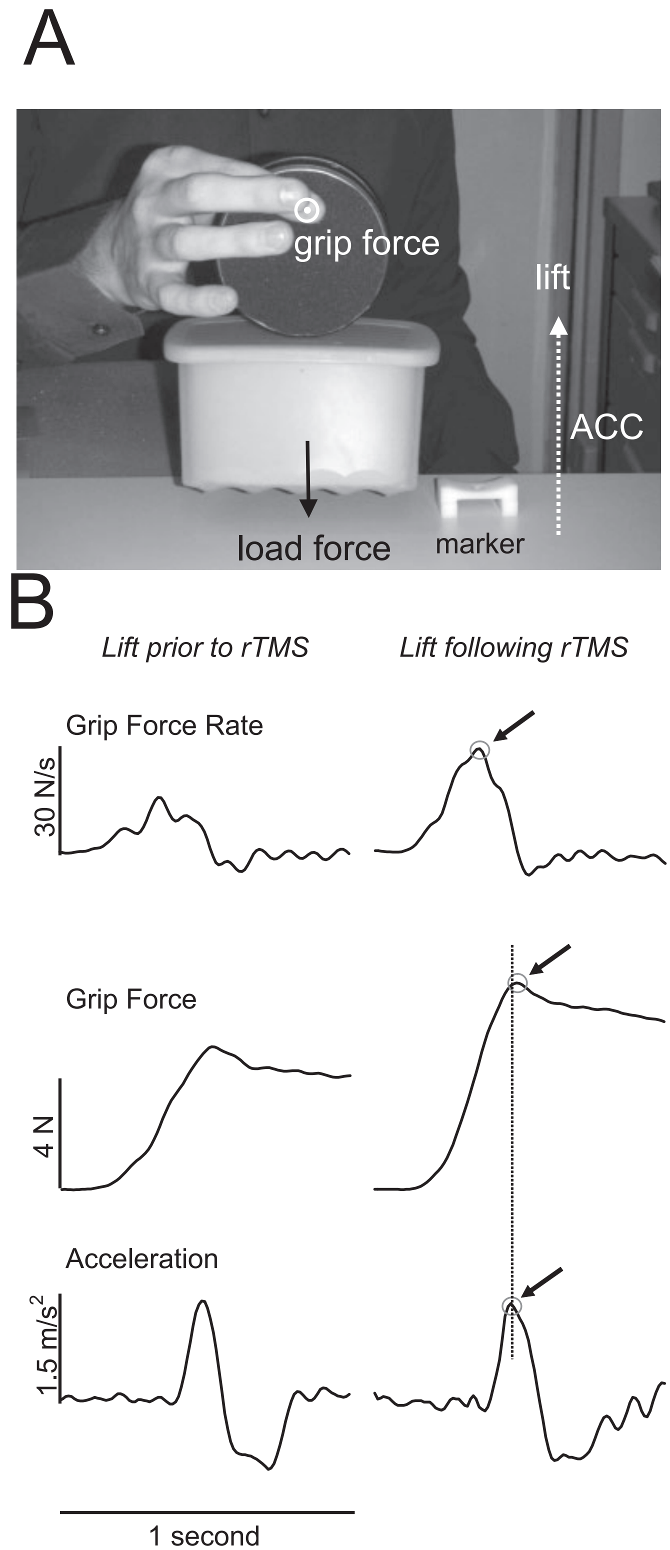

FIG. 1. (A) The instrumented object incorporated a force sensor to register grip force and linear acceleration sensors to measure accelerations in three dimensions. ACC, kinematic acceleration in the direction of lifting. (B) Traces of grip force rate, grip force and vertical acceleration from single lifts performed with the dominant hand immediately prior to (left panels) and following (right panels) 20 s of repetitive high-frequency transcranial magnetic stimulation (rTMS) over M1. The arrowheads indicate the parameters obtained for data analysis: maximum rate of grip force development, maximum grip force and maximum acceleration. The peak grip force occurs closely in time with peak acceleration (dotted vertical line).

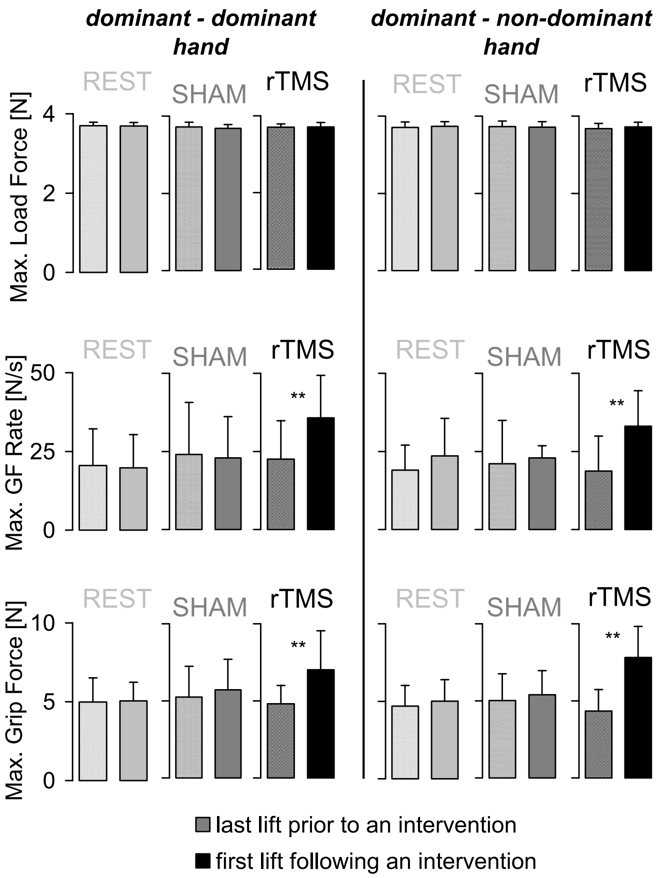

FIG. 2. Average values (+ one standard deviation) of peak load forces, peak rates of grip force increase and peak grip forces established at the lift performed immediately prior to and following an intervention [repetitive high-frequency transcranial magnetic stimulation (rTMS), sham and motor rest]. Lifts performed with the dominant hand prior to and following an intervention are illustrated in the left-handed panels; lifts performed with the dominant hand prior to and with the non-dominant hand following an intervention are illustrated in the right-handed panels. $^{**}P < 0.001$.

stimulation the magnetic coil was placed vertically on the scalp so that the lateral aspect of the coil touched the scalp and the magnetic field ran tangentially to the scalp. Each subject performed a series of 10 consecutive lifts with between-lift intervals of ~ 5 s. After completion of 10 lifts, subjects received either rTMS over the dominant M1, sham stimulation of M1 or they simply rested both hands for 20 s on a cushion placed on their lap. After 20 s of rTMS, sham stimulation or motor rest subjects performed another series of 10 lifts. Four subjects started with rTMS, four with sham stimulation and four with motor rest. After a 10-min break and completion of 10 more lifts, subjects received another intervention and performed another series of 10 lifts. This procedure was repeated until three sets of 20 lifts, each separated by one of the three interventions, had been performed.

Experiment 2: effects of rTMS on grip force scaling at the non-dominant hand

This experiment addressed the question of possible effects of: (i) rTMS; (ii) sham stimulation; or (iii) motor rest transfer across hands. Subjects first performed 10 lifts with their dominant hand. After a 20 s intervention (rTMS, sham stimulation or rest) they performed another series of 10 lifts with the non-dominant hand. Four subjects started with rTMS, four with sham stimulation and four with motor rest. After a 10-min break and completion of 10 more lifts with the dominant hand, another intervention was applied followed by another series of 10 lifts with the non-dominant hand. The procedure was repeated until three sets of 20 lifts separated by one of the three interventions were completed.

Data analysis

Figure 1B illustrates traces of grip force rate, grip force and acceleration for lifts performed with the dominant hand prior to and following rTMS. We determined: (i) maximum rate of grip force development; (ii) maximum load force (load force was calculated from the product of object mass and the vectorial summation of gravity and inertial acceleration due to lifting); and (iii) the maximum grip force. The maximum rate of grip force development occurs prior to lift-off, as signalled by the acceleration sensor in the lift axis. The ratio of maximum grip force to maximum load was calculated to obtain a measure of the efficiency of grip force scaling. Statistical evaluation should assess the influence of rTMS, sham stimulation and motor rest on predictive force scaling. Separate repeated-measures analysis of variance were performed on each dependent variable with the between-subject factors ‘treatment’ (rTMS, sham stimulation and motor rest) and the within-subject factors ‘sequence’ (dominant–dominant hand, dominant–non-dominant hand) and ‘time’ (lift before and after an intervention). *T*-tests were used for *post-hoc* pair-wise comparisons. *P*-values less than 0.05 after Bonferroni correction were considered statistically significant.

Results

The average minimum grip forces (± standard deviations) were 1.78 (± 0.1) N and 1.76 (± 0.2) N for the dominant and non-dominant hands, respectively ($P = 0.65$). Figure 2 shows mean values of peak load forces, peak grip force rates and peak grip forces established during lifts immediately prior to and following an intervention.

Effects of rTMS on peak load force

The peak load forces were of similar magnitude prior to and following an intervention, regardless of the intervention or the hand performing the lift. Indeed, none of the factors ‘time’, ‘treatment’ or ‘sequence’, or their interactions (e.g. interaction ‘time’ × ‘treatment’: $P = 0.28$) had a significant effect on peak load forces. This is an important observation indicating that the kinematics of the lifting movement, performed by more proximal arm muscles, was not affected by each of the three factors.

Effects of rTMS on peak rate of grip force development

The peak rates of grip force development increased after rTMS ($P < 0.001$), but not after the hands were at rest or after sham stimulation. In fact, the influence of rTMS on the peak force rates produced after the intervention differed in comparison to the effects of motor rest ($P < 0.001$) or sham stimulation ($P < 0.001$). rTMS increased the peak force rates similarly for lifts performed with the dominant and non-dominant hands: the increase in peak force rate at the first lift following rTMS in relation to the lift immediately preceding rTMS was 57% (22.6–35.8 N/s) for the sequence dominant–dominant hand and 77% (18.7–33.1 N/s) for the sequence dominant–non-dominant hand. In conclusion, rTMS, but not sham stimulation or a period of motor rest, disturbed the predictive grip force development.

Effects of rTMS on peak grip force

The peak grip forces increased for lifts after rTMS ($P < 0.001$), but not after sham stimulation or motor rest. The effect of rTMS on peak grip forces generated after rTMS differed in comparison to the effects of motor rest ($P < 0.001$) or sham stimulation ($P < 0.001$), suggesting that rTMS, but not sham stimulation or motor rest, disturbs predictive grip force scaling. The effects of rTMS on peak grip forces were similar for lifts performed with the dominant and non-dominant hands: the increase in peak grip force at the lift following rTMS in relation to the lift immediately preceding rTMS was 46% (4.8–7 N) for the sequence dominant–dominant hand and 80% (4.3–7.8 N) for the sequence dominant–non-dominant hand.

rTMS not only affected the first lift following the intervention, but also caused subjects to squeeze the object more forcefully at all lifts following rTMS. Peak grip force at the 10th lift following rTMS was still significantly higher than that produced at the lift immediately preceding rTMS, regardless of hand sequence ($P < 0.01$ for all comparisons). The peak grip forces decreased from the first to the 10th lift of a series performed prior to and following each intervention (comparison of peak grip forces produced at lift 1 vs. lift 10: $P < 0.04$ for rTMS; $P < 0.001$ for break; $P < 0.01$ for sham stimulation). Thus, subjects were able to adjust the grip force output more accurately with increasing number of lifts performed.

Effects of rTMS on grip–load force ratio

The ratios between peak grip and load forces increased after rTMS ($P < 0.001$), but not after motor rest or sham stimulation. The effect of rTMS on the force ratios differed in comparison to that of motor rest ($P < 0.001$) or sham stimulation ($P < 0.001$). Thus, rTMS hampers accurate grip force scaling that had been established over the preceding set of lifts. The influence of rTMS was similar for lifts performed with the dominant and non-dominant hands: the increase in force ratios at the lift following rTMS in relation to the lift immediately preceding rTMS was 46% (1.3–1.9) for the sequence dominant–dominant hand and 78% (1.2–2.1) for the sequence dominant–non-dominant hand.

Discussion

Our data show that 20 s of rTMS applied over the hand area of the dominant M1 increases the grip force output when next lifting a familiar object. Moreover, the force output remained elevated over the following set of lifts, suggesting that rTMS disrupts predictive grip force processing for a several-minute period. These effects were not observed when subjects rested both hands on their lap or when a sham stimulation was applied for the same period of time. Interestingly, the disruptive effect of rTMS on predictive force scaling transferred across hands, suggesting transcallosal transfer of information in between both hemispheres (Gordon *et al*., 1994). Importantly, rTMS over the hand area of M1 did not influence the lifting forces exerted by more proximal arm muscles.

Recently, another group demonstrated that 15 min of subthreshold 1 Hz rTMS over M1 disrupted the scaling of grasping forces based on information acquired during a set of five lifts (Chouinard *et al*., 2005). Our data extend these previous results in several ways: first, we show that only 20 s of our rTMS protocol over M1 produces a similar disruption of predictive force scaling. Second, we observed a significant effect of rTMS not only on the grip force rate, a measure of force prediction, but also on the ratio between grip and load forces, a measure of the effectiveness of force scaling. Third, in contrast to previous data, our rTMS protocol had no influence on peak lift forces generated by more proximal arm muscles, suggesting that the disruptive effect is more precisely focused to the hand. Finally, we measured grip forces immediately after rTMS, whereas Chouinard *et al*. (2005) gave several sets of single-pulse TMS over M1 between rTMS and the next series of lifts. These single TMS pulses evoked MEPs in the hand, the amplitude of which was used to measure the effectiveness of rTMS conditioning. Unfortunately, the MEP-induced movements may have influenced predictive grip force scaling as any movement (Flanagan & Johansson, 2002; Quaney *et al*., 2003), even illusory movement (Nowak *et al*., 2004), of the hand performing the task influences the grip force applied in subsequent lifts.

When we repeatedly lift a novel object we are able to establish a highly efficient grip force scaling within a few lifts (Johansson & Westling, 1988). The established memory link between the object properties and the grip force is termed sensorimotor memory. Several investigations tested how this memory is influenced by preceding voluntary actions, such as single lifts of an object with novel mechanical properties (Johansson & Westling, 1988) or squeezing an unrelated object (Quaney *et al*., 2003). We demonstrate that rTMS to M1 disrupts predictive grip force processing when lifting a familiar object. Interestingly, grip force was scaled down after the first lift, but remained elevated above baseline throughout the entire set of lifts following rTMS. It appears that rTMS over M1 affects the efficacy of its inputs, such as input from sensory receptors as well as voluntary effort, but not the establishment of short-term sensorimotor memory related to the most recent lift.

If an internal model related to the mechanical object properties was used to programme grip force, then a period of rTMS over M1 might have changed the model characteristics. M1 is located in close anatomical vicinity to S1, and there is evidence from neurophysiology and neuroimaging that both cortical areas form a single functional locus (SM1) for the sensorimotor control of movement (Lemon, 1981; Naito *et al*., 2002). Probably, our rTMS protocol also interferes with the neural processing in S1. Such interference may occur directly, via current spread to S1, or indirectly, via functional interconnections between M1 and S1. Consequently, rTMS may hamper the integration of actual sensory input from the grasping fingers, the formation of the corollary discharge signals, the planning and execution of the descending motor commands or a combination of all these options. The observation that the disruptive effects of rTMS over M1 transferred across hands gives strong support to the idea that the sensorimotor memory related to the most recent lift is lateralized to one hemisphere depending on the hand performing the lift (Gordon *et al*., 1994).

Our preliminary data suggest that rTMS over the hand area of M1 disturbs predictive grip force planning, while it does not interfere with the processing of motor commands to more proximal arm muscles. Future studies have to address the issue if the observed effect of rTMS on predictive grip force specification holds true in a wider context of object manipulation.

Abbreviations

M1, primary motor cortex; MEPs, motor-evoked potentials; rTMS, repetitive high-frequency transcranial magnetic stimulation.

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