Magnifying the View of the Hand Changes Its Cortical Representation. A Transcranial Magnetic Stimulation Study

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Abstract

■ Changes in the perceived size of a body part using magnifying lenses influence tactile perception and pain. We investigated whether the visual magnification of one's hand also influences the motor system, as indexed by transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEPs). In Experiment 1, MEPs were measured while participants gazed at their hand with and without magnification of the hand. MEPs were significantly larger when participants gazed at a magnified image of their hand. In Experiment 2, we demonstrated that this effect is specific to the hand that is visually magnified. TMS of the left motor cortex did not induce an increase of MEPs when participants looked at their magnified left hand. Experiment 3 was performed to determine if magnification altered the topography of the cortical representation of the hand. To that end, a 3 × 5 grid centered on the cortical hot spot (cortical location at which a motor threshold is obtained with the lowest level of stimulation) was overlaid on the participant's MRI image, and all 15 sites in the grid were stimulated with and without magnification of the hand. We confirmed the increase in the MEPs at the hot spot with magnification and demonstrated that MEPs significantly increased with magnification at sites up to 16.5 mm from the cortical hot spot. In Experiment 4, we used paired-pulse TMS to measure short-interval intracortical inhibition and intracortical facilitation. Magnification was associated with an increase in short-interval intracortical inhibition. These experiments demonstrate that the visual magnification of one's hand induces changes in motor cortex excitability and generates a rapid remapping of the cortical representation of the hand that may, at least in part, be mediated by changes in short-interval intracortical inhibition. ■

INTRODUCTION

Information regarding the size and shape of the body plays a crucial role in perception and action (Medina & Coslett, 2010, 2016). This effect is evident, for example, in the phenomenon of "visual enhancement of touch" (VET) in which vision of the hand improves two-point discrimination performance (Taylor-Clarke, Jacobsen, & Haggard, 2004; Kennett, Taylor-Clarke, & Haggard, 2001), spatial localization of tactile stimulation (Press, Taylor-Clarke, Kennett, & Haggard, 2004), and perception of grating orientation (Fiorio & Haggard, 2005). Importantly, in studies demonstrating VET, participants are prevented from viewing the location on the body to be touched, but nonetheless, the vision of the hand significantly influences task performance. In addition, increasing the apparent size of the body with magnifying lenses improves performance in tactile discrimination tasks (Taylor-Clarke et al., 2004; Haggard, Taylor-Clarke, & Kennett, 2003; Kennett et al., 2001). Kennett et al. (2001) presented adults with a two-point discrimination task for unseen tactile stimuli on the forearm. When participants viewed their forearm as magnified, performance was significantly more accurate as compared with viewing the normal size forearm. Similarly, Taylor-Clarke et al. (2004) examined how visual magnification of a body part influences Weber's illusion, which states that the distance between two tactile stimuli will be perceived as greater if the stimuli are applied on a body area with higher tactile acuity (like the finger) compared with a region with lower sensitivity (like the forearm). Weber's illusion was markedly reduced in participants after 1 hr of visual training viewing a distorted vision of their own hand, with the forearm magnified and the hand minimized.

The "magnification effect" is not confined to tactile discrimination but also extends to pain perception (Mancini, Longo, Kammers, & Haggard, 2011; Moseley, Parsons, & Spence, 2008). The effects of changes in the apparent size of a body part, using magnifying or minimizing lenses, have been tested in both patients with chronic pain and normal participants. In patients with chronic pain, Moseley et al. (2008) reported an increase of the level of pain if participants saw the hand magnified. Mancini et al. (2011) used the mirror box technique and thermal stimulation to measure pain thresholds when participants were looking at the hand or an object

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in normal, magnified or minimized vision. Participants showed a higher pain threshold when looking at their hand as compared with the object. Perceived body size modulated the pain thresholds: Higher temperatures were required to induce pain stimulation when the hand was seen magnified, whereas minimized view of the hand reduced the pain threshold. Evidence of changes in action performance with magnification or minimization of a body part has been reported in studies investigating movement kinematics (Bernardi et al., 2013; Karok & Newport, 2010; Marino, Stucchi, Nava, Haggard, & Maravita, 2010). These studies demonstrated that magnification of the hand altered reaching and grasping parameters. With magnification of the hand, grip aperture is smaller compared with normal viewing of the hand or no vision of the hand (Bernardi et al., 2013; Karok & Newport, 2010; Marino et al., 2010), whereas movement times were shorter when the hand was viewed as larger (Karok & Newport, 2010). Recent work suggested that this modulation of action performance with the magnification of hand size depends on the level of visual information available regarding vision of the hand and the target of the action, as young adults are able to adjust their movement performance to changes in vision when visual feedback is available (Ambron, Schettino, Coyle, Jax, & Coslett, 2017).

A number of conclusions can be drawn from this literature. First, the occurrence of the magnification effect suggests that the online representation of the body that mediates sensory perception and action is malleable and integrates multiple sensory inputs (Medina & Coslett, 2010, 2016; Haggard et al., 2003; Kennett et al., 2001). It has been proposed that multimodal parietal areas might be involved in this process, providing feedback to unimodal somatosensory areas (Kennett et al., 2001). Second, as body magnification has an effect on motor performance (Bernardi et al., 2013; Karok & Newport, 2010; Marino et al., 2010), it may induce changes not only in somatosensory areas but also in the motor cortex.

We report the first investigation of which we are aware of examining the effect of visual magnification of a body part on primary motor cortex. Experiment 1 tested whether the magnification of a body part through vision induces an increase of cortical excitability in motor cortex. Experiment 2 assessed whether the increased motor cortex activation is specific to the magnified body part. Experiment 3 explored the hypothesis that magnification alters motor cortex topography and creates a rapid remapping of cortical representation of the hand area. Finally, Experiment 4 sought to determine if the influences of magnification on motor cortex excitability were mediated by inhibitory and excitatory influences on M1. To test these hypotheses, we used transcranial magnetic stimulation (TMS) and recorded motor evoked potentials (MEPs) from an intrinsic hand muscle while participants were looking at their hand in normal vision or with magnifying lenses.

GENERAL PROCEDURE

Participants

All participants in this study were (i) right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971), (ii) between 18 and 50 years old, and (iii) without history of neurological disorders. All participants signed an informed consent before starting the experiment, and the study was approved by the institutional review board of the University of Pennsylvania.

Pretesting Phase

Each experiment included a pretesting phase for each participant that identified the optimal cortical site in the left hemisphere for eliciting MEPs from the right abductor pollicis brevis (APB; Experiment 1) or right first dorsal interosseous (FDI; Experiments 2 and 3). This "hot spot" was defined as the cortical site at which an MEP for the target muscle could be elicited with the lowest stimulation intensity (Groppa et al., 2012). This hot spot was marked on the participant's structural MRI scan or on a structural MRI template (Experiment 2) using Brainsight software (Rogue Research) and was used as the target area in Experiments 1, 2, and 4 and as the center of the stimulation grid in Experiment 3. TMS was performed using Magstim 200^2 monophasic stimulator in Experiments 1–3; paired-pulse stimulation was delivered using Magstim BiStim System in Experiment 4. A 70-cm "figure-of-eight" coil placed tangentially to participants' scalp and tilted 45° from the body midline was used to elicit MEPs in all experiments.

EMG was used to record MEPs from the APB or FDI and to identify the resting motor threshold (rMT) of each participant. rMT was defined as the percentage of machine output that elicited MEPs on at least 5 of 10 trials. EMG signals were recorded using disposable Ag/AgCl electrodes in a belly–tendon montage. The signal was amplified and sampled at 1000 Hz. The signal was filtered using a two-pole Butterworth filter with 1 Hz as low-pass and 1000 Hz as high-pass filter and with AC couple and 60-Hz Notch, using a CED 1902 Signal Conditioner (Cambridge Electronic Design).

Data Extraction and Analysis

MEPs were measured offline using Signal 3.1.3 as the peak-to-peak amplitude of the response to each stimulation. For all experiments, each waveform was visually assessed for each participant; approximately 3% of trials were eliminated because of signal noise or poor quality waveform. In Experiments 1–3, the mean MEP amplitude for each stimulated site was calculated for all trials across all conditions of the experiment. For each stimulation site, outliers, defined a priori as values more than 2 standard deviations (*SD*s) from the grand mean MEP from that site, were excluded. Finally, in Experiment 4, outliers

were identified independently for the different types of stimulation (unconditioned [UNC], short-interval intracortical inhibition [SICI], intracortical facilitation [ICF]) as responses, which differed by more than 2 *SD*s from the overall mean of that stimulation condition.

The analyses of the hot spot in Experiments 1–3 were conducted on the peak-to-peak amplitude data, whereas for all other analyses of Experiments 2 and 4, logarithmic transformations were applied to peak-to-peak amplitude data as they improved the normality of the MEP distribution. Data were analyzed using linear mixed-effects models computed in R (version 3.3.0) and LMER packages (lmerTest and lme4) run on trial-by-trial data. First, we created a series of models in which factors and interactions between factors of interest were inserted sequentially. Second, models were compared using log-likelihood ratio tests, and the final, optimized model comprised only factors contributing significantly to the model fit. Third, we calculated conditional R^2 value for the optimized model (Johnson, 2014). We controlled for the nonindependence of repeated measures within subjects by inserting subject as a random intercept in all the models; fixed factors and interactions used in model testing varied across experiments. These were as follows: in Experiments 1 and 2, condition (PRE, MAG, POST); in Experiment 3, condition (PRE, MAG, POST) and group (1,2,3,4) of stimulated sites defined on the basis of the distance from the hot spot; and in Experiment 4, condition (PRE, MAG, POST) and type of stimulation (SICI and ICF). For descriptive purposes, raw data rather than the log-transformed are plotted in the graphs.

EXPERIMENT 1

Experiment 1 consisted of single-pulse stimulation to the APB hot spot to investigate whether hand magnification increases MEP amplitude.

Methods

Seventeen neurologically intact, right-handed individuals participated (nine women; mean age = 22.3, range = 19–27). Participants underwent three blocks of 40 single-pulse TMSs each. In the first block (PRE condition), participants were asked to look at the dorsum of their right hand, which was resting comfortably on a table and situated at the body midline. In the second block, they looked at the dorsum of their right hand through a 2.2× magnifying lens (MAG condition); in the last block, they were tested again in normal vision (POST condition). TMSs were delivered at 120% of the rMT with an interval of 4–7 sec between stimulations. Blocks of trials were separated by 2- to 3-min rest intervals.

Results

In Experiment 1, a model including condition (PRE, MAG, POST) as the only fixed factor and subjects as a random factor estimated MEP amplitude better than the baseline model containing by-subjects random intercepts only (logLik = −5395; $\chi^2(5) = 14.8$, $p < .001$; $R^2 = .70$). As shown in Figure 1A, MEP amplitude was higher in the MAG condition compared with both the PRE ($t(1916) = -3.0$, $p = .002$) and POST ($t(1916) = -3.5$, $p < .001$) conditions; but similar performance was observed between PRE and POST ($t(1916) = -0.50$, $p = .61$).

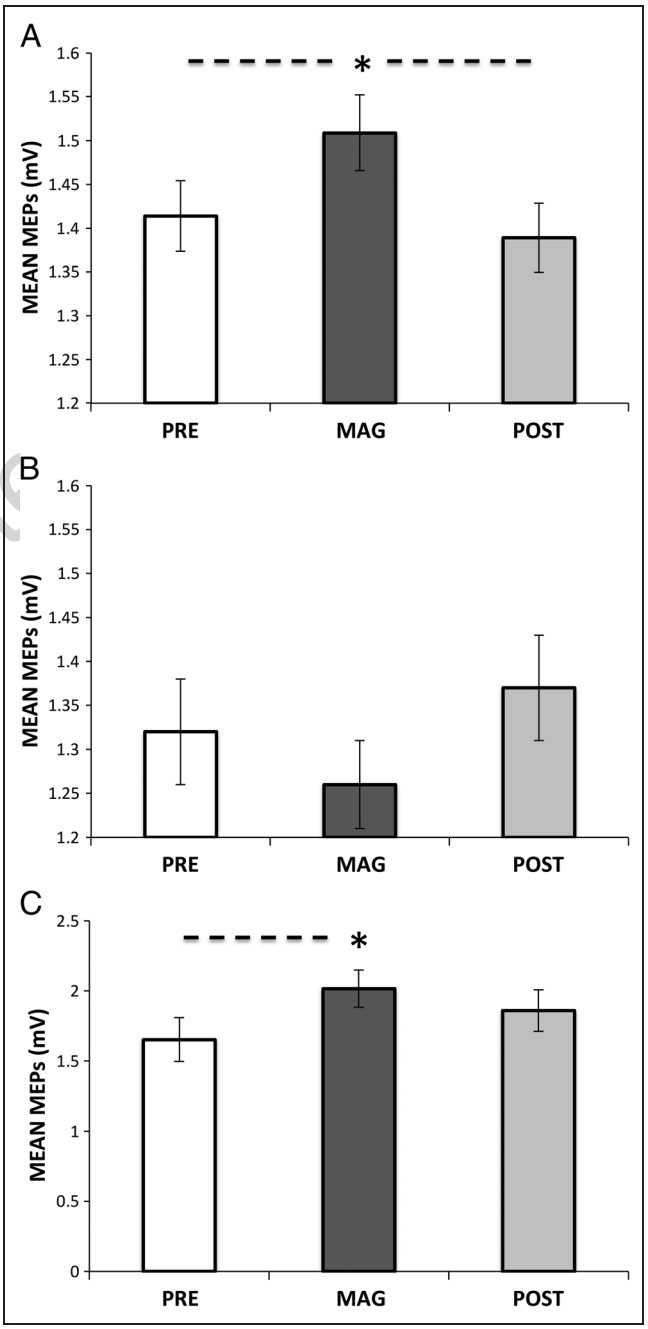

Figure 1. Mean of peak-to-peak amplitude in the PRE, MAG and POST conditions in (A) Experiment 1, (B) Experiment 2, and (C) Experiment 3. The error bars represent the standard errors.

Discussion

Visual magnification of the hand (MAG condition) increased MEP amplitude compared with a normal vision baseline (PRE condition), but the effect quickly reversed with restoration of normal vision (POST condition). This finding demonstrates that magnification increases cortical excitability in M1 relative to normal viewing. At least three different accounts could explain these data. First, magnification may induce a rapid enlargement of the cortical representation of the magnified body part, allowing for recruitment of more corticospinal neurons activating the target muscle. Second, magnification may increase the excitability of M1 neurons such that the same neurons are stimulated in the MAG condition but respond more vigorously.

There is precedent for the view that body part representations in sensory and motor cortex can be rapidly modified (Sawaki et al., 2008; Braun et al., 2001; Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995). Furthermore, there is ample evidence of changes in M1 topography after deafferentation (e.g., Werhahn et al., 2002; Brasil-Neto et al., 1992), amputation of the hand (Fuhr et al., 1992; Cohen, Bandinelli, Findley, & Hallett, 1991), or motor training (Liepert et al., 1998); in these situations, there is an increase in cortical areas representing the hand, as well as an increase in MEP amplitude.

Accounts 1 and 2 differ with respect to the cortical location of the effect. If magnification increases the size of the cortical representation of the hand, one would expect to elicit larger MEPs in regions around the hot spot with magnification. In contrast, if magnification enhances the responsiveness of the same neuronal population, one would expect no change in responsiveness except at the hot spot. We return to this issue in Experiment 3.

Finally, the observed modulation of the cortical excitability might reflect a nonspecific response to the novelty of the altered visual input. On this interpretation, the increase in MEP amplitude with magnification would not reflect change in the brain area representing the magnified body part but rather an increase of the cortical excitability related to the novelty of altered visual input. If the increase in MEPs is a general effect related to novelty or arousal, one would expect a similar enhancement of MEPs in conditions in which vision is magnified but participants are looking at a different body part or at an object. In contrast, if the increase in MEPs is generated by an alteration in the excitability of M1 that is specific to the magnified body part, one would expect no change in MEPs with magnification of the other hand. We tested this interpretation in Experiment 2.

EXPERIMENT 2

Experiment 2 was performed to determine if the increase in MEP with magnification of the hand observed in Experiment 1 reflected a nonspecific effect of change in vision or a body part specific change in M1 excitability. To this end, participants were presented with a similar setup as in Experiment 1, but they looked at the left hand in normal and magnified vision, rather than at the stimulated hand (right hand).

Methods

Ten neurologically intact, right-handed individuals (10 women, mean age = 20, range = 18–26) who had not participated in Experiment 1 underwent three blocks of 40 single-pulse TMSs to the APB hot spot in the left motor cortex. Participants gazed at the dorsum of their left hand (ipsilateral to the TMS) in normal (PRE condition), magnified with 2.2× lenses (MAG condition), and normal (POST condition). Participants' right hand rested on their right thigh and was covered with a black cloth so that only the left hand was visible. As in Experiment 1, stimulation was delivered at 120% of the rMT with an interval of 4–7 sec between stimulations.

Results

The model including condition (PRE, MAG, POST) as the only fixed factor and subjects as a random factor did not differ significantly from a baseline model containing by-subjects random intercepts only (logLik = −1483; $\chi^2(2) = 4, p = .13$; $R^2 = .51$), suggesting that condition did not have a significant effect on MEP amplitude. As shown in Figure 1B, similar MEP amplitude was observed across conditions.

Discussion

Experiment 2 showed that magnification of vision alone does not induce a significant change in the cortical excitability in M1, even if the magnification involves a body part, and the body part in question is the hand. These data argue strongly against a novelty and/or arousal account of the results of Experiment 1 and suggest that increasing the perceived size of a body part increases cortical excitability in the brain area representing the magnified body part.

EXPERIMENT 3

In Experiment 3, we explored the possibility that magnification of the hand results in an increase in the size of the cortical representation of the hand. If this is true, one would expect that MEPs would be elicitable from a larger region with magnification of the hand. To that end, a 3 × 5 grid of stimulation sites was centered on the hot spot, and single-pulse TMS was administered to all 15 sites in the grid. If magnification increases the cortical representation of the muscle, one would expect higher MEPs to be generated from a larger number of sites on the grid. Alternatively, if magnification increased

the responsiveness of the same pool of neurons generating the response with normal vision, one would not expect to see an increase in responsiveness from other sites.

Methods

Thirteen right-handed young adults (seven women, mean age = 22.2, range = 19–30) were recruited; these subjects had not participated in Experiment 1 or Experiment 2. As the aim of this experiment was to test whether visual magnification of the hand would change the cortical representation of this body part, we first identified the FDI hot spot. Using this as the center, we employed Brainsight software to generate a grid consisting of three columns and five rows for a total of 15 stimulation sites; the long axis of the grids was approximately parallel to the central sulcus. Each location was marked by a 1-mm circle and was separated by 7 mm in both the superior and inferior dimensions (see Figure 2). Sites were numbered as depicted in Figure 2.

Single TMS pulses at 120% of the rMT were used to stimulate each position of the grid; MEPs were recorded from the FDI on all trials. There were four blocks of 75 trials. In the first block, participants looked at the dorsum of their right hand during TMS (PRE condition). In the following two blocks, participants viewed their hand through the 2.2× magnifying lens used in Experiment 1 (MAG condition), and in a final block, they viewed their hand in normal vision (POST condition). In each block, every position of the grid (n = 15) was stimulated five consecutive times (75 stimulation per block) at an interval of 4–7 sec between stimulations. For each participant, the order of stimulation of the different sites was randomized within and between blocks. MEP amplitude was calculated for each trial as described above.

Results

A series of linear mixed-effects models analyses were carried out to investigate (i) whether we replicated the results of Experiment 1 at the hot spot and (ii) whether magnification altered MEP amplitude at sites other than the hot spot.

To address the first issue, we tested a model with condition as a fixed factor and subjects as a random intercept for the hot spot MEP amplitude data. This model explained significantly more variance than the initial model containing by-subjects random intercepts only (logLik = −292.6; $\chi^2(5) = 10.9$, $p = .004$; $R^2 = .71$). As shown in Figure 1B, we found a similar pattern of MEP amplitude as in Experiment 1, with a significant increase in the peak-to-peak amplitude from the PRE to MAG conditions ($t(233) = 3.3$, $p = .001$). In the POST condition, MEP amplitudes were lower than, but not significantly different from, the MAG condition ($t(233) = 1.6$, $p = .09$) and did not significantly differ from the PRE condition ($t(233) = t = -1.23$, $p = .17$).

A second analysis was performed using data from the 14 locations surrounding the hot spot (see Table 1). For this purpose, sites were grouped as a function of the distance from the hot spot. There were two groups of sites: The first group included the sites 7 mm (Sites 7, 9, 5, 11) and the sites 9.8 mm from the hot spot (Sites 4, 6, 10, 12), and the second group included the sites at a distance of 15 mm (Sites 2 and 14) and of 16.5 mm (Sites 1, 3, 13 and 15) from the hot spot. Group was inserted as fixed factor in the model together with condition. This model proved to explain significantly more variance in the data than the model, with condition as the only fixed factor (logLik = −4721.2; $\chi^2(1) = 360.9$, $p < .001$; $R^2 = .52$).[1] Across groups, we observed a similar pattern of MEP amplitude as for the hot spot, with higher MEP amplitude observed in the MAG ($M = 1.44$, $SE = 0.03$) than PRE ($M = 1.24$, $SE = 0.04$) or POST ($M = 1.39$, $SE = 0.04$) conditions. Overall, MEP amplitude decreased as function of the distance from the hot spot (Group 1: $M = 1.64$, $SE = 0.03$; Group 2: $M = 1.01$, $SE = 0.02$). Looking at the differences across blocks in the specific groups, we observed an increase of MEP amplitude from the PRE to MAG conditions ($t(3453) = 2.2$, $p = .026$) in Group 1 and also in Group 2 ($t(3453) = 4.9$, $p < .001$). MEP amplitude was higher in the POST than PRE conditions for Group 2 ($t(3453) = 4.4$, $p < .001$) and marginally for Group 1

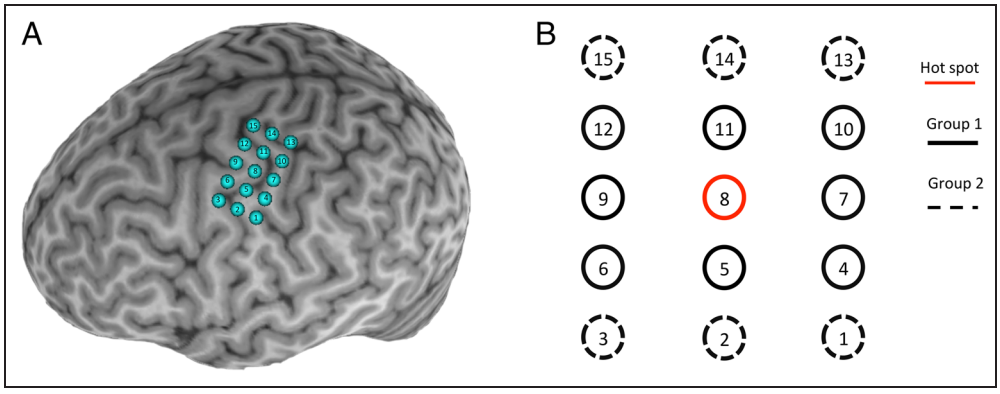

Figure 2. (A) Representation of the grid in Brainsight. (B) Numbering of the grid and subdivision in groups of sites.

Table 1. Means and *SE* of the MEPs for Each Site of Stimulation in the PRE, MAG, and POST Conditions

	PRE		*MAG*		*POST*	
	M	*SE*	*M*	*SE*	*M*	*SE*
Site 1°	0.54	0.07	0.95	0.07	0.84	0.07
Site 2+	0.77	0.08	0.93	0.07	1.22	0.15
Site 3°	0.64	0.06	0.89	0.06	0.81	0.09
Site 4*	1.31	0.14	1.71	0.11	1.48	0.16
Site 5#	1.51	0.17	1.69	0.11	1.58	0.15
Site 6*	1.53	0.16	1.71	0.13	1.49	0.13
Site 7#	1.38	0.16	1.74	0.13	1.73	0.17
Site 9#	1.72	0.22	1.85	0.13	2.00	0.22
Site 10*	1.37	0.18	1.28	0.13	1.44	0.20
Site 11#	1.62	0.20	1.83	0.15	1.68	0.20
Site 12*	1.82	0.21	1.83	0.14	1.75	0.15
Site 13°	0.94	0.14	0.99	0.11	0.95	0.15
Site 14+	1.14	0.18	1.33	0.14	1.14	0.13
Site 15°	1.10	0.16	1.41	0.13	1.42	0.14
Distance 1#	1.53	0.06	1.70	0.04	1.64	0.06
Distance 2*	0.85	0.05	1.08	0.04	1.05	0.05

($t(3453) = 1.8$, $p = .06$). Finally, similar MEP amplitude was observed between the MAG and POST conditions for both Group 1 ($t(3453) = -0.14$, $p = .88$) and Group 2 ($t(3453) = 0.22$, $p = .82$).

Similar effects were also observed when looking at the single sites of stimulations (see Table 1 for mean and *SE* of MEPs for each site and block and Figure 3 for a graphical representation).

Discussion

This experiment yielded two main findings. First, magnifying the image of the hand from which MEPs were recorded increases MEP size at the hot spot, replicating and extending our findings from Experiment 1. It should be noted that the same effect was observed with stimulation of the hot spot for the APB (Experiment 1) and FDI (Experiment 3), suggesting that the magnification influences the representation for the entire magnified hand rather than a single muscle. Second, magnification increases MEPs across a number of sites in addition to the hot spot in M1. MEP amplitude was higher in the MAG condition than in the PRE condition, not only at the hot spot but also in regions surrounding the hot spot; in fact, significant increases were observed up to a distance of 16.5 mm from the hot spot.

One difference was noted between the effects in Experiments 1 and 3. In the latter, the effect of magnification persisted into the POST condition, as shown by the higher MEPs at both hot spot and surrounding regions in the POST than PRE conditions. We speculate that this is caused by differences in the number of stimuli delivered with magnification in the two experiments. In Experiment 1, there were only 40 stimuli with magnification, whereas in Experiment 3, magnification was present for 150 stimuli. Thus, one possible explanation for the persistence of magnification effects in Experiment 3 is that the longer duration and larger number of stimuli presented

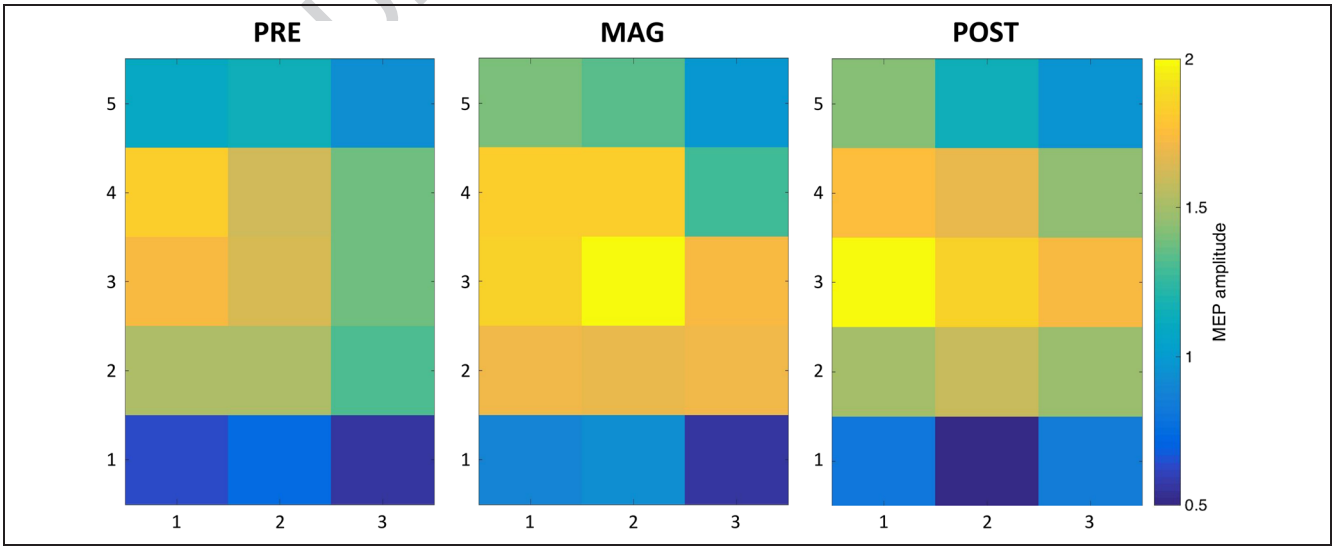

Figure 3. Means of peak-to-peak amplitude across all the sites of stimulation in the PRE, MAG, and POST conditions. Each heat map has a spatial correspondence with the grid with the *y* axes indicating the rows and the *x* axes indicating the columns of the grid.

with magnification may have generated more long-lasting effects.

These results support the hypothesis that magnification induces an increase in the size of the cortical representation of the hand. These results support the hypothesis that magnification induces an increase in the cortical representation of the hand. The mechanism by which this effect is achieved, however, is not clear. One possibility is that magnification of the hand alters the online connections between a population of pyramidal cells in M1 and muscles of the hand; on this account, MEPs recorded from intrinsic hand muscles are larger with magnification because a greater number of cortical neurons, perhaps including those on the periphery of the nonmagnified hand representation, are at least temporarily linked to hand muscles. An alternative account is that magnification increases MEPs recorded from intrinsic hand muscles because it enhances the excitability of the population of motor neurons in the cortex corresponding to the magnified hand. Assuming a variable distribution of motor neuron excitability in the hand motor representation at rest, an intervention that increases the level of resting activation across the population of motor neurons would increase MEPs because TMS would depolarize a larger number of motor neurons in a population with a higher average level of excitability. It is possible, of course, that both mechanisms are at play. Unfortunately, our data do not permit us to distinguish between these (and other) accounts.

The finding that magnification alters the motor representation of the hand is not without precedent. The present pattern of data mirrors the increase in cortical representation of the motor cortex observed after motor training (Pascual-Leone et al., 1995), upper limb amputation (Cohen et al., 1991), and temporary ischemic nerve block (Werhahan et al., 2002; Brasil-Neto et al., 1992). It has been proposed that the mechanism underlying this effect may be the creation of new cortical connections or the unmasking of preexisting connections (Ziemann, Hallett, & Cohen, 1998; Pascual-Leone et al., 1995). The demonstration that alterations in cortical responsiveness occur after only minutes of magnification suggests that the effects reported here are attributable to unmasking of preexisting patterns of connectivity rather than the creation of new networks.

The hypothesis that magnified vision of the hand induces an increase in the cortical representation of that body part raises the question of the secondary effect of this cortical reorganization on neighboring areas. For example, studies of individuals with phantom limb suggest that the expansion of the cortical representation of the face occurs at the expense of the representation of the missing limb (see Ramachandran & Altschuler, 2009, for a review). If the cortical remapping observed in this study follows similar principles, we would predict that the MEP amplitude measured from body parts represented in proximity to the hand (e.g., arm or face) in M1 would decrease when participants look at their hand magnified rather in normal vision, whereas this effect should not be observed in MEPs recorded from muscles represented at a distant location from the hand area (e.g., foot). As the main focus of the present work was to show that the magnification of the hand induces changes in cortical excitability in the representation of the hand, we did not investigate how this cortical reorganization affects other regions. This could be explored in future investigations.

We note that stimulation sites close to the hot spot had slightly larger MEPs than the hot spot in the PRE and POST conditions (see Figure 3). The explanation for this is not clear. It is possible that altering the topography of the motor representation alters the "center of mass" of the population of motor neurons generating the MEP, thereby slightly altering the location of the "hot spot." As the number of stimuli delivered to each of the 15 locations was smaller in Experiment 3 as compared with the number of stimuli delivered to the hot spot in Experiments 1 and 2, it is possible that this represents a sampling artifact. Our statistical analysis was performed on groups of sites with a similar distance from the hot spot to minimize such artifacts. Data presented in Figure 3 were reported for illustrative purposes.

EXPERIMENT 4

One potential mechanism underlying the effects reported here is that magnification alters local inhibitory and excitatory inputs to corticospinal tract pyramidal cells. Intracortical inhibition and facilitation, dependent on GABAergic and glutamatergic neurotransmission, respectively (Ziemann et al., 1996), are assumed to modulate cortical excitability. Studies exploring cortical changes after amputation (Chen et al., 1998), deafferentation (Ziemann et al., 1998), and motor training (Perez, Lungholt, Nyborg, & Nielsen, 2004; Nordstrom & Butler, 2002) propose that reduction of GABAergic inhibition would unmask cortical connections and induce cortical remapping.

There is also precedent for the hypothesis that intracortical inhibition and excitation are relevant to vision-induced changes in sensory motor function. Cardini, Longo, Driver, and Haggard (2012) measured somatosensory evoked potentials while participants performed a tactile discrimination task looking at their hand or at an object. Vision of the hand induced a suppression of the P50, suggesting that vision induces an increase in cortical inhibition. Following this reasoning, the increase in lateral inhibition would reduce the tactile receptive fields and provide a better spatial accuracy in tactile discrimination task. Although the issue has not been explored in the motor system, the finding of Cardini et al. (2012) raises the possibility that magnification might induce similar mechanisms in M1.

In Experiment 4, we used paired-pulse TMS techniques to explore the role of intracortical inhibition and

facilitation in the genesis of magnification effects. Based on data from Cardini et al. (2012), we predicted that magnification effects in motor function would be associated with increased intracortical inhibition.

Methods

Fourteen right-handed individuals (seven women, mean age = 25.1, range = 18–52) participated in an experiment with UNC, SICI, and ICF trials. In SICI, a conditioning pulse inhibits the MEP amplitude of the test pulse. In contrast, ICF results in larger MEP amplitudes than in the UNC test pulse. The degree of inhibition or facilitation can be measured as the ratio of conditioned (that is, SICI or ICF) MEP amplitude to UNC MEP amplitude. There were four blocks of 45 trials: in Blocks 1 (PRE condition) and 4 (POST condition), participants viewed the dorsum of their right hand in normal vision, whereas in Blocks 2 and 3 (MAG condition), they viewed their right hand through 2.2× magnifying lenses. In each block, 45 trials of three types of TMS (15 trials each) were delivered in random sequence. In the UNC, single-pulse stimulations were delivered at 120% of rMT. In SICI and ICF conditions, a conditioning stimulus (S1) presented at 80% rMT was followed by the test stimulus (S2) at 120% rMT. ISIs were 3 msec for SICI and 10 msec for ICF. Peak-to-peak amplitude data of SICI and ICF conditions were recoded as a ratio of the UNC stimulation for each participant. This was done for each block separately by dividing single MEP response of the SICI and ICF from the mean of UNC MEP in that block.

Results

Linear mixed-effects models analysis showed that the model including both stimulation type and condition as fixed factors and subjects as a random intercept improved the model fit with respect to a model with only stimulation type as a fixed factor and subjects as a random intercept (logLik = −835.8; $\chi^2(4) = 11.1$, $p = .017$; $R^2 = .39$). As shown in Figure 4, the ratio of SICI to UNC trials was less than 1 in all conditions, whereas the ratio of ICF to UNC trials was greater than 1 in all conditions. For the SICI stimulation, the ratio decreased from the PRE to MAG conditions ($t(1534) = -2.3$, $p = .021$) and marginally in the POST condition ($t(1534) = -1.7$, $p = .08$). No differences were observed between the MAG and POST conditions ($t(1534) = 0.33$, $p = .7$). For the ICF, the ratio was higher in the POST than both PRE ($t(1534) = 2.18$, $p = .029$) and MAG conditions ($t(1534) = 1.9$, $p = .053$). Ratios in the PRE and MAG conditions did not differ ($t(1534) = 0.6$, $p = .52$).

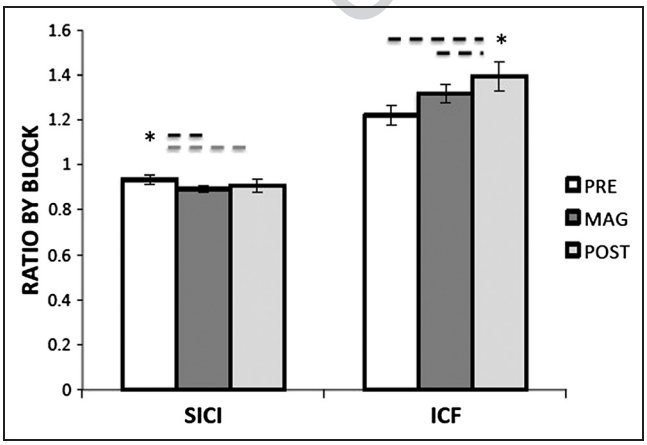

Figure 4. Ratio of MEPs for SICI (left) and ICF (right) stimulation in the PRE, MAG, and POST conditions. For the SICI, lower values indicate higher intracorticial inhibition. For the ICF, higher values indicate higher intracorticial facilitation.

Discussion

We expected magnification of the hand to induce changes in cortical inhibition and/or ICF. We found a progressive increase in ICF across conditions, but these differences reached a significant level only in the comparison between the POST condition and both the MAG and PRE conditions. The fact that, in the previous experiments and in Experiment 1 in particular, we observed that MEPs decline after magnification whereas, in the present, experiment ICF increases at this point suggests that this change does not account for the magnification effect on MEPs.

We found a significant change in intracortical inhibition that roughly paralleled the MEP data of Experiment 3; that is, magnification was associated with a lower level of SICI, reflecting an increase in intracortical inhibition; like the effects on MEP amplitude, this effect only partially reversed in the POST block. The parallel between MEP amplitude changes and levels of intracortical inhibition is consistent with the hypothesis that magnification effects are mediated, at least in part, by changes in intracortical inhibition and that these effects outlast the magnification. The correspondence between the changes in MEP amplitude and intracortical inhibition suggests that the latter may be relevant to the changes in MEP amplitude with magnification. One might speculate that the increase in intracortical inhibition represents an adaptive, homeostatic response; as fine, graded action is dependent on a balance of cortical excitation and inhibition, the enhanced motor cortex excitability induced by magnification may evoke an increase in cortical inhibition that serves to partially offset the effects of magnification. We note that the direction of the change in intracortical inhibition is in line with Cardini et al. (2012), who found an increase of cortical inhibition in the somatosensory cortex when the vision of hand was magnified.

On the other hand, the present results are in contrast with studies showing a reduction of SICI with limb amputation (Chen et al., 1998) or deafferentation (Ziemann

et al., 1998), or as a consequence of training (Perez et al., 2004; Nordstrom & Butler, 2002). It must be acknowledged that the association between reduced SICI and changes in the motor representation has not been confirmed in this study (Chen, Anastakis, Haywood, Mikulis, & Manktelow, 2003), and it is possible that the two phenomena might be independent.

GENERAL DISCUSSION

Although magnification of visual input improves motor performance, the neural basis of this effect has not been established. In Experiment 1, we demonstrate for the first time that magnification of the hand rapidly and reversibly increases cortical excitability in M1 for that body part. Experiment 2 demonstrated that these effects occur specifically in the brain region corresponding to the magnified body part. In Experiment 3, we replicated the effects of magnification on the cortical hot spot and demonstrated that MEP amplitudes were increased at sites distant to the hot spot. These data are consistent with the hypothesis that the benefits of magnification derive from an increase in the cortical resources devoted to the body part. Finally, in an attempt to identify the mechanism by which the effects of magnification are mediated, in Experiment 4 we assessed the effects of intracortical inhibition and facilitation; we demonstrate that magnification of the hand results in an increase in intracortical inhibition.

Our data derive from interrogation of M1; we suggest, however, that the visual effects on motor performance reflect differences in processing at multiple sites in the network integrating sensory and motor function. One possible explanation is that the effects reported here are mediated by multimodal parietal areas (Kennett et al., 2001). This account has precedent in a study investigating the VET (Konen & Haggard, 2014). In this study, participants were required to look at an object or at their hand for 100 msec, followed by a period of darkness and a grating discrimination task. TMS was applied over the anterior intraparietal sulcus (aIPS) or the sensory motor hand area in two different occasions: after the visual or tactile stimuli. A disruption of the VET was observed when TMS was applied over sensorimotor area only if the stimulation occurred after the tactile stimulus presentation. On the contrary, TMS over the aIPS immediately after the visual stimulation (0–300 msec) disrupted the VET, but not when this area was targeted after the tactile stimulation. This evidence suggests that multimodal parietal areas, including aIPS, may function as multisensory integration sites with strong reciprocal connections to primary somatosensory and visual cortices (Haggard et al., 2003). Alternatively, these effects could be related to a direct pathway connecting visual and motor cortices (Makin, Holmes, Brozzoli, & Farnè, 2012), responding to rapid changes in action-relevant visual information (Makin, Holmes, Brozzoli, & Farnè, 2009). The present results do not allow one to adjudicate between these two hypotheses, and future work should test the possible role of the intraparietal sulcus in the magnification effect.

The explanation for an increase in intracortical inhibition as measured by SICI in the setting of increased MEPs is not clear. It should be noted, however, that MEP amplitudes reflect transynaptic activation of pyramidal neurons and are influenced by multiple factors. TMS activates presynaptic elements, including axon collaterals of pyramidal tract neurons, afferent fibers from the thalamus or striatal projections, intracortical interneurons, and association fibers from other cortical areas such as somatosensory and premotor regions (Terao & Ugawa, 2002). We speculate that magnification of the hand increases pyramidal neuron output directly (thus increasing MEP amplitude) and also increases the output of inhibitory and interneuron circuits (leading to increased SICI with magnification). The fact that MEPS are increased with magnification may speak to the balance between these contrasting effects. One might speculate that the observed increase in intracortical inhibition represents a homeostatic mechanism implemented to temper the excitatory effects of magnification.

To conclude, we demonstrate that increasing the apparent size of body parts does not simply improve perceptual processing in normal participants (Taylor-Clarke et al., 2004; Kennett et al., 2001) but induces changes in the cortical excitability and in the cortical topography of the magnified body parts. The ability to modulate motor function directly and reversibly using a simple and safe intervention raises the possibility that multimodal integration phenomena such as we report may prove to have clinical implications.

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Note

1. As we were interested in the interaction between group and conditions, we reported the comparison between this model and the condition-only model. However, the model with the interaction did not differ from the model with the main effects of group and conditions (logLik = −4720.7; $\chi^2(2) = 1.9$, $p = .56$).

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