Corticospinal excitability is enhanced after visuomotor adaptation and depends on learning rather than performance or error

Hamid F. Bagce,1,2 Soha Saleh,1,2,3 Sergei V. Adamovich,1,2,3 John W. Krakauer,4 and Eugene Tunik1,2

1Department of Rehabilitation and Movement Science, School of Health Related Professions, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; 2Graduate School of Biomedical Sciences, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; 3Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, New Jersey; and 4Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland

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Bagce HF, Saleh S, Adamovich SV, Krakauer JW, Tunik E. Corticospinal excitability is enhanced after visuomotor adaptation and depends on learning rather than performance or error. J Neurophysiol 109: 1097–1106, 2013. First published November 28, 2012; doi:10.1152/jn.00304.2012.—We used adaptation to high and low gains in a virtual reality setup of the hand to test competing hypotheses about the excitability changes that accompany motor learning. Excitability was assayed through changes in amplitude of motor evoked potentials (MEPs) in relevant hand muscles elicited with single-pulse transcranial magnetic stimulation (TMS). One hypothesis is that MEPs will either increase or decrease, directly reflecting the effect of low or high gain on motor output. The alternative hypothesis is that MEP changes are not sign dependent but rather serve as a marker of visuomotor learning, independent of performance or visual-to-motor mismatch (i.e., error). Subjects were required to make flexion movements of a virtual forefinger to visual targets. A gain of 1 meant that the excursions of their real finger and virtual finger matched. A gain of 0.25 (“low gain”) indicated a 75% reduction in visual versus real finger displacement, a gain of 1.75 (“high gain”) the opposite. MEP increases (>40%) were noted in the tonically activated task-relevant agonist muscle for both high- and low-gain perturbations after adaptation reached asymptote with kinematics matched to veridical levels. Conversely, only small changes in excitability occurred in a control task of pseudorandom gains that required adjustments to large errors but in which learning could not accumulate. We conclude that changes in corticospinal excitability are related to learning rather than performance or error.

Sensorimotor cortex; primary motor cortex; transcranial magnetic stimulation; motor evoked potential; virtual reality

The performance versus learning distinction is a particularly vexing issue when studying changes in the brain after training in healthy subjects or in patients (Krakauer 2007). One approach to assessing the state of the motor system is to measure corticospinal excitability with transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEPs) (Pascual-Leone et al. 1994, 1995; Muellbacher et al. 2001). MEPs serve both as an assay for internal changes in inhibitory/excitatory balance that cannot be accessed directly and as a measure of the integrity of a motor output pathway. For example, a lower conduction time (Vang et al. 1999), a higher baseline MEP amplitude (Rapisarda et al. 1996), and a greater change in MEP amplitude (Koski et al. 2004; Swayne et al. 2008) after stroke are thought to be beneficial to voluntary action, i.e., performance. Alternatively, increases in MEP have been associated with motor learning (Cirillo et al. 2011; Gallasch et al. 2009; Jensen et al. 2005; Koenke et al. 2006) rather than changes in motor output, although in these studies the learning-related changes in performance were not controlled for. One study, however, demonstrated that as subjects learned to increase peak pinch force to maintain a target electromyographic (EMG) profile, motor cortex excitability scaled up in a linear fashion (Muellbacher et al. 2001). On follow-up measurements, MEP amplitude returned to baseline levels but subjects retained the learned peak force profile, which suggested that the increased MEP was not necessary to maintain performance but instead was associated with learning. Alternative explanations for the excitability changes in this study are possible, however. One is that the transient increase in MEP amplitude was a result of the ramping up of force (i.e., motor output) from low to high (versus high to low) during adaptation, rather than learning per se. Another potential explanation is that the increased excitability was the result of error: once the mismatch between produced and optimal force was zero, excitability normalized. Thus whether excitability changes are truly learning related rather than related either to the direction of the change in the magnitude of motor output or to errors remains unresolved.

Here we sought to test directly whether learning affects corticospinal excitability, independent of performance or error, by studying gain adaptation of finger movements in a novel virtual reality (VR) environment. Gain adaptation is ideally suited to testing the competing hypotheses that changes in M1 excitability relate to changes in performance or error versus that they relate to learning. In the low-gain condition (gain = 0.25) a 75% reduction in visual versus real finger displacement occurs, requiring an increase in finger excursion, whereas the high-gain condition (gain = 1.75) results in the opposite. It has been shown that some motor cortical cells linearly scale firing rate with speed and distance (Paninski et al. 2004). As a gain change requires either a higher or a lower peak velocity and displacement for a given visual excursion compared with baseline, M1 excitability changes might reflect changes in firing rate. That there is a relationship between excitability and firing rate has been known from classic animal studies investigating the effect of anodal DC current on motor cortex...
excitability could be attributed to a learned remapping and not just keep subjects engaged in the task. To ensure that any change in angles (45°/65°/85°, 14 trials per angle). Three targets were used to block consisted of 42 movements performed toward three physical experiment 4 (9 men, 5 women; 26.8 ± 6.2 yr). All subjects were right-handed (Oldfield 1971) and free of neurological or orthopedic conditions that could interfere with the experiment, were safe to receive TMS (Keel et al. 2000), and provided written and verbal institutionally informed consent. All protocols were approved by the Institutional Review Board of the University of Medicine and Dentistry of New Jersey.

MATERIALS AND METHODS

Subjects

Nine subjects participated in experiment 1 (5 men, 4 women; mean ± SD age 25.9 ± 4.6 yr), 9 in experiment 2 (5 men, 4 women; 29.2 ± 7.0 yr), 6 in experiment 3 (4 men, 2 women; 32.0 ± 6.9 yr), and 14 in experiment 4 (9 men, 5 women; 26.8 ± 6.2 yr). Subjects were seated with forearms (semipronated) and hands hidden from direct line of sight under a widescreen monitor oriented horizontally (Fig. 1B). Real-time visual feedback of hand motion was conveyed on the monitor as motion of VR-rendered hand models (Virtools software; Dassault Systems) actuated by kinematic data streaming from data gloves (5DT-16MRI) worn by subjects. The display was angled and magnified such that VR hand size, position, and orientation matched a first-person perspective vantage.

Task

Upon a visual cue, subjects flexed the right index finger metacarpophalangeal (MCP) joint to a virtual target represented on the screen as an arrow (i.e., subjects were asked to completely cover the virtual arrow with the virtual finger) and then returned to a fully extended position. Subjects were asked to complete the task as fast as possible, but without sacrificing accuracy or precision. Each trial lasted 3.5 s (intertrial rest interval: 2.5 s). Depending on the experiment (see below), the motion of the VR hand was scaled in real time relative to the kinematic data streaming from the glove. One of three scaling factors was applied to the VR hand motion: 1.00 (G1.00, veridical), in which virtual hand motion corresponded to actual motion, 0.25 (G0.25), in which virtual hand motion was 25% of actual motion, and 1.75 (G1.75), in which virtual hand motion was 175% of actual motion (Fig. 1A). Thus a 45° actual movement would produce a virtual movement of 11.25° (G0.25), 45° (G1.00), or 78.75° (G1.75).

Experiment 1. This experiment tested for changes in corticospinal excitability following a block of adaptation to low-gain visual feedback. Subjects performed the task in three blocks. Feedback was G1.00 in block 1 and G0.25 in block 2 (Fig. 1C, top). Each block consisted of 42 movements performed toward three physical angles (45°/65°/85°, 14 trials per angle). Three targets were used to keep subjects engaged in the task. To ensure that any change in excitability could be attributed to a learned remapping and not just changes in movement amplitude, movements were kinematically clamped, which is to say that subjects’ physical target angles were 45°, 65°, and 85° at the end of adaptation. This was achieved through systematic manipulation of the perceived angular position of the target
in virtual space: it was either kept the same (G1.00 blocks: 45°/65°/85°) or adjusted to be of smaller visual excursion (G0.25 block: 11.25°/16.25°/21.25°). As detailed below, MEPs were measured after each movement block.

**Experiment 2.** This experiment tested for changes in corticospinal excitability following a block of adaptation to high-gain visual feedback. The protocol was similar to experiment 1, except here movement amplitude in all three blocks was clamped at 20°/30°/40°, with visual excursion reaching 20°/30°/40° in G1.00 and 35°/52.5°/70° in G1.75. The nature of the high-gain visual feedback was the reason why different movement amplitudes were used in experiment 2. For example, implementing an 85° movement amplitude in experiment 2 would have required an unnatural 148.75° virtual joint angle.

**Experiment 3.** This was a control experiment to address the potential confound that changes in MEPs might relate to progressive increases in peak velocity (i.e., motor output) associated with gain adaptation rather than learning per se. Subjects performed movements with veridical feedback in three separate blocks. During blocks 1 and 3 (B1G1.00, B3G1.00), subjects made 42 movements to one of three pseudorandomly presented target angles (35°/45°/55°). During block 2 (B2G1.00), on the other hand, the target angle was increased from 10° to 55°, simulating a “ramping up” of motor output throughout the block. To prevent subjects from anticipating subsequent targets during block 2, angles of 5° increments were pseudorandomly presented in a progressively increasing fashion throughout block 2 (i.e., 10°...20°...15°...30°...). The last 10 trials during block 2 were identical to blocks 1 and 3, ensuring that subjects reached similar asymptotic levels of motor output.

**Experiment 4.** The block experiments described above were designed to test the hypothesis that corticospinal excitability changes are the result of accumulated learning rather than motor output. A counterhypothesis would be that these changes arise because of perceived errors and their associated corrections. This control experiment tested excitability during trial-by-trial error correction in the absence of a constant systematic perturbation that would allow accumulation oflearning. Subjects flexed the MCP joint over a single block (66 total trials). In pseudorandomly interleaved trials, feedback was G1.00, ensuring that subjects reached similar asymptotic levels of motor output.

Coil position.

To ensure that coil position did not differ among conditions, a three-way rmANOVA with factors time [early, late], target [angle1, angle2, angle3], and condition [B1Veridical, B2Gain, B3Veridical] was calculated. The first and last trials for each angle of each condition were used for the “early” and “late” data, respectively. For kinematic analysis of experiment 3,
Fig. 2. Kinematic and electrophysiological data in experiment 1. A (subject): blue line and shaded region represent the mean (±SD) metacarpophalangeal (MCP) flexion angle (top) and peak angular velocity (middle) for a typical subject, averaged across B1G1.00 and B3G1.00. Mean traces of the first 3 (early, solid red) and last 3 (late, dashed red) trials of B2G0.25 are superimposed. Mean (±SD) MEP bar plot (bottom) for this subject demonstrates increased M1 facilitation immediately after B2G0.25 relative to B1G1.00 and B3G1.00. B (group): group mean (±SE) peak velocity as % change relative to the average veridical trials for each angle for each block. Trials for all 3 target angles are binned together; thus the 42 total trials are represented by 14 bins on the x-axis. Subjects adapted to B2G0.25 by normalizing movement velocity to the level observed in the veridical blocks. Also shown (inset) is group mean (±SE) MEP.

RESULTS

Excitability Increased After Gain Adaptation

Subjects showed complete adaptation to visuomotor gain when visual motion of the VR finger was scaled to either 25% (experiment 1, G0.25 condition) or 175% (experiment 2, G1.75 condition) of actual finger motion. Figure 2A (experiment 1) and Figure 3A (experiment 2) show a representative subject’s mean joint angle (top) and angular velocity (middle) traces for early and late adaptation stages. While early adaptation was characterized by initial hypometria (experiment 1) or hypermetria (experiment 2) with subsequent online adjustments, finger position traces during late adaptation were comparable to those in the veridical block. For kinematic analysis of experiments 1 and 2 a three-way rmANOVA with factors [levels]: time [early, late], target [angle1, angle2, angle3], and condition [B1Veridical, B2Gain, B3Veridical] was calculated. The first and last trials for each angle of each condition were used for the early and late data, respectively. For kinematic analysis of experiment 3, a one-way rmANOVA with levels [B1Veridical, B2Veridical, B3Veridical] was calculated for both early- and late-stage adaptation, in which the average of the first and last three trials was used for the early and late data, respectively. It should be noted that in experiment 2 there was a significant drop in peak velocity below baseline at around trial 8 (see 3rd time bin in Fig. 3B), likely due to subjects’ tendency in early trials to overshoot the visual target but in later trials to adjust online kinematics by moving at a slower speed. We quantified the degree of adaptation by calculating the peak velocity in each trial. Figure 2B and Figure 3B show similar behavior at the group level, in which subjects progressively adapted their peak velocity to match that of the veridical blocks. As expected, rmANOVA revealed a significant main effect of target angle on peak velocity for both the low- and high-gain learning paradigms (experiment 1: F_{2,16} = 122.41,
P < 0.001; experiment 2: F(2,16) = 40.73, P < 0.001). Notably, a significant main effect of visual feedback condition on peak velocity was observed for both the low- and high-gain learning paradigms (experiment 1: F(2,16) = 11.94, P = 0.002; experiment 2: F(2,16) = 4.36, P = 0.038), and, as displayed in Figs. 2B and 3B, the time × condition interaction effect was also significant (experiment 1: F(2,16) = 5.552, P = 0.016; experiment 2: F(2,16) = 5.29, P = 0.023). To confirm that the observed effects were a result of learning, we averaged raw velocities across all three angles and performed two separate one-way rmANOVAs for both the early and late interactions. Subanalysis revealed a significant main effect of visual feedback condition on peak velocity during the early stage of adaptation (experiment 1: F(2,16) = 20.208, P < 0.001; experiment 2: F(2,16) = 6.438, P = 0.011); however, similar effects were not seen during the latter phase of each block (experiment 1: F(2,16) = 1.073, P = 0.363; experiment 2: F(2,16) = 1.171, P = 0.334), suggesting that subjects fully adapted to the visuomotor gain. Post hoc pairwise comparison confirmed that velocity effects were driven by significant differences between the early gain block and first veridical block (Tukey’s corrected; experiment 1: t8 = -4.038, P = 0.001; experiment 2: t8 = 3.4685, P = 0.004) but not between the two veridical blocks (Tukey’s corrected; experiment 1: t8 = -2.277, P = 0.10; experiment 2: t8 = -0.294, P = 0.221). Overall, these findings demonstrate that kinematic performance in finger space after adaptation was similar to that seen before adaptation.

MEPs were measured in the FDI muscle for a period of 2 min following each training block. Representative subject (Figs. 2A and 3A) and group data (Figs. 2B and 3B) demonstrate that corticospinal excitability was increased for a period of 2 min after adaptation to both low- and high-gain feedback (mean percent change ± SE: experiment 1: 53.3 ± 16.2%; experiment 2: 40.9 ± 17.1%) relative to the veridical. rmANOVA confirmed a significant MEP effect for both experiments (experiment 1: F(2,16) = 4.618, P = 0.026; experiment 2: F(2,16) = 4.901, P = 0.042). Post hoc pairwise comparisons revealed that the effects were driven by significant differences between MEPS following the adaptation block and MEPS following the first veridical block (Tukey’s corrected; experiment 1: t8 = 2.694, P = 0.044; experiment 2: t8 = 2.511, P = 0.038) but not when comparing MEPS following the first and second veridical blocks (Tukey’s corrected; experiment 1: t8 = -0.035, P = 0.999; experiment 2: t8 = -0.021, P = 1.000). No significant between-condition differences were noted in background EMG activity (experiment 1: F(2,16) = 2.321, P = 0.147; experiment 2: F(2,16) = 0.647, P = 0.519), suggesting that any difference in motor output could not account for the MEP effects.

We performed a post hoc subanalysis of MEPS collected after the low-gain (experiment 1) and high-gain (experiment 2) blocks to discern whether postadaptation increases in excitability were relatively stable over the entire 2 min of MEP data collection. Pairwise t-tests revealed nonsignificant differences between the first and last 10 MEPS following both the low-gain block (MEP ± SE: early: 2.27 ± 0.48 mV; late: 2.26 ± 0.47 mV, t8 = 0.070, P = 0.946) and the high-gain block (MEP ± SE: early: 2.63 ± 0.44 mV; late: 2.30 ± 0.37 mV, t8 = 1.286, P = 0.234), suggesting that only a slight drop in excitability occurred during the second half of MEP data collection.

We performed a second post hoc analysis on MEP and EMG variance to ensure that the above effects were not driven by outlier trials. For this, the variance of these two outcome measures (MEP and EMG) was calculated for each experiment (experiment 1 and experiment 2) for each subject (S1 through S9) for each condition (veridical-gain-veridical). Variances were submitted to a rmANOVA, which confirmed no significant main effect of condition on MEP variance (experiment 1: F(2,16) = 0.16, P = 0.850; experiment 2: F(2,16) = 1.50, P = 0.253) or EMG variance (experiment 1: F(2,16) = 1.49, P = 0.255; experiment 2: F(2,16) = 0.88, P = 0.432).

Finally, to ensure an appropriate sampling size for the remaining experiments (experiments 3 and 4), we performed a sample-size calculation for the two primary outcome variables (MEPs and angular velocity) of experiments 1 and 2, using an ANOVA with a significance threshold set to 0.05 and a power of 0.8. To be more conservative, we used data from the high-gain adaptation experiment (experiment 2), which had the smaller effects in both variables. For an effect size of 2.61 [MEPs: (2.38 – 1.78)/0.23] and 4.15 [velocity: (2.32 – 1.78)/0.13], the sample-size calculation indicated a minimum of 5 and 3 subjects, respectively, to yield significant effects.

**Control Experiment: “Ramping Up” Motor Output Did Not Augment Excitability.**

We performed a control experiment (experiment 3) to rule out the possibility that the postadaptation M1 excitability increases observed in experiments 1 and 2, which were in the same direction (increases), were the result of the similar “ramping up” of peak velocity (i.e., motor output) to the final asymptotic level. Figure 4 shows that peak velocity in B2G1.00 pseudorandomly increased to the asymptotic level of B1G1.00 and B3G1.00 (velocity early: F(2,10) = 30.632, P < 0.001; velocity late: F(2,10) = 1.300, P = 0.309). Figure 4, inset, shows that when M1 excitability was probed at the end of each block we observed no between-block MEP effects (F(2,10) = 0.605, P = 0.565), suggesting that increases in M1 excitability

![Fig. 4. Kinematic and electrophysiological data in control experiment 3 (see MATERIALS AND METHODS). Labels are as in Fig. 2B. Gold color shows the incrementally increasing angular velocity over the course of the block, without any requirement for visuomotor adaptation (as was necessary in experiments 1 and 2). Note the absence of any modulation of M1 excitability at the group level (inset).](http://jn.physiology.org/doi/10.1152/jn.00304.2012)
Significantly differed between conditions (F1,110 = 5.934, P = 0.011) but not between the G1.75 and G1.00 conditions (P = 0.993). Thus only small MEP effects were seen in the trial-by-trial experiment compared with the blocked paradigm despite larger perceived errors and continuous corrections in velocity. The effect seen in the low-gain condition is likely a small learning effect because we still found a small MEP effect after binning the trials.

MEPs were evoked online as the subjects’ actual MCP angle reached 40°. Figure 5A, bottom (typical subject), and Fig. 5B, right (group mean), show that MEP amplitude was affected by visual feedback (main effect: F2,26 = 5.934, P = 0.008). Post hoc pairwise comparisons confirmed that the 12.1% (±2.9) MEP increase was significant in the G0.25 over the G1.00 condition (t13 = 2.965, P = 0.011) but not between the G1.75 and G1.00 conditions (P = 0.993). Thus only small MEP effects were seen in the trial-by-trial experiment compared with the blocked paradigm despite larger perceived errors and continuous corrections in velocity. The effect seen in the low-gain condition is likely a small learning effect because we still found a small MEP effect after binning velocity across conditions. To do this, G0.25 trials with velocities exceeding 1 SD and G1.75 trials with velocities below 1 SD of each individual subject’s global mean velocity were excluded from analysis (rmANOVA for angular velocity after trial exclusion: F2,26 = 1.080, P = 0.348).

Despite equalized velocity across all three visual feedback conditions, the possibility remains that these changes in excitability resulted from a period of observing and correcting errors in movements to a 45° physical angle. Three different visual gains were pseudorandomly interleaved across trials: veridical (G1.00), low gain (G0.25) or high gain (G1.75). Figure 5A shows a typical subject’s mean joint angle (top) and angular velocity (middle) trace for each condition. Instantaneous angular velocity immediately prior to the TMS pulse (i.e., at 40° flexion) was calculated to confirm that subjects showed kinematic evidence of a differential response to the gain changes. At the group level (see Fig. 5B, left), angular velocity significantly differed between conditions (F2,26 = 18.843, P < 0.001), with post hoc pairwise comparisons revealing that subjects significantly sped up in the G0.25 condition (group mean = 1.996 rad/s, t13 = 3.187, P = 0.007) and slowed down in the G1.75 condition (1.531 rad/s, t13 = 4.270, P = 0.001), relative to the veridical condition (G1.00: 1.822 rad/s). Thus subjects were seeing large errors in every trial and attempted to correct them. We confirmed this further by analyzing peak angular acceleration in the first 100 ms of the subsequent (n + 1) trial (i.e., before visual feedback contaminated the feedforward plan developed in the n trial). Significant differences were noted for the n + 1 trials (mean ± SE for G1.00, G0.25, and G1.75: 12.6 ± 1.1 rad/s², 13.3 ± 1.1 rad/s², 11.5 ± 0.9 rad/s²; F2,26 = 4.418, P = 0.023), with post hoc comparisons demonstrating a slight, although nonsignificant, increase in acceleration for post-G0.25 trials (t13 = 1.25, P = 0.232) and a slight decrease for post-G1.75 trials (t13 = 1.58, P = 0.139), relative to post-G1.00 but a significant difference between post-G0.25 and post-G1.75 trials (t13 = 3.14, P = 0.008). This suggests that subjects partially preplanned movements based on the feedback they received in the previous trial. A control analysis of the same kinematic variable for trials preceding the G1.00, G0.25, and G1.75 (“n − 1”) trials, as expected, did not show this effect (12.0 ± 0.9, 12.6 ± 1.1, 12.8 ± 1.1 rad/s²; F2,26 = 1.897, P = 0.174). These kinematic analyses revealed that subjects were overtly responding online to the observed visual errors and partially adapting to each perturbation, evidenced by the n + 1 analysis, although they never reached full adaptation because of the pseudorandom ordering of the trials.

Values are group mean (±SE) kinematic and electrophysiological data. MEP, motor evoked potential during the motor task; Vel, peak angular velocity.

Table 1. Summary of group mean kinematic and electrophysiological data for experiment 1 (low-gain adaptation)

<table>
<thead>
<tr>
<th></th>
<th>B1G1.00</th>
<th>B2G0.25</th>
<th>B3G1.00</th>
</tr>
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<tbody>
<tr>
<td>MEP, mV</td>
<td>1.615 ± 0.382</td>
<td>2.262 ± 0.473</td>
<td>1.625 ± 0.394</td>
</tr>
<tr>
<td>EMG, mV</td>
<td>0.031 ± 0.005</td>
<td>0.037 ± 0.007</td>
<td>0.030 ± 0.004</td>
</tr>
<tr>
<td>Vel, rad/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>2.189 ± 0.134</td>
<td>1.614 ± 0.106</td>
<td>2.464 ± 0.096</td>
</tr>
<tr>
<td>Late</td>
<td>2.692 ± 0.220</td>
<td>2.418 ± 0.222</td>
<td>2.719 ± 0.268</td>
</tr>
</tbody>
</table>

Values are group mean (±SE) kinematic and electrophysiological data. MEP, motor evoked potential after the motor task; Vel, peak angular velocity. Peak velocity is averaged across all 3 target angles.

Table 2. Summary of group mean kinematic and electrophysiological data for experiment 2 (high-gain adaptation)

<table>
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<tr>
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<th>B1G1.00</th>
<th>B2G1.75</th>
<th>B3G1.00</th>
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<tr>
<td>MEP, mV</td>
<td>1.778 ± 0.229</td>
<td>2.380 ± 0.327</td>
<td>1.781 ± 0.261</td>
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<tr>
<td>EMG, mV</td>
<td>0.054 ± 0.012</td>
<td>0.061 ± 0.013</td>
<td>0.051 ± 0.009</td>
</tr>
<tr>
<td>Vel, rad/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>1.780 ± 0.130</td>
<td>2.317 ± 0.148</td>
<td>1.825 ± 0.088</td>
</tr>
<tr>
<td>Late</td>
<td>1.971 ± 0.173</td>
<td>1.857 ± 0.192</td>
<td>2.031 ± 0.145</td>
</tr>
</tbody>
</table>

Values are group mean (±SE) kinematic and electrophysiological data. MEP, motor evoked potential after the motor task; Vel, peak angular velocity. Peak velocity is averaged across all 3 target angles.
conditions, MEP amplitude remained 12.2% higher in the G0.25 condition (rmANOVA for MEP after trial exclusion: $F_{2,26} = 3.931, P = 0.038$).

To characterize the relative contribution of each independent variable to MEP amplitude, we performed a mixed linear regression analysis. MEPs were significantly correlated with expected variables such as coil displacement error ($\beta = -0.194, P < 0.001$), background EMG ($\beta = 0.212, P = 0.001$), and the G0.25 condition ($\beta = 0.120, P = 0.003$) but not with angular velocity ($\beta = 0.041, P = 0.262$) or the G1.75 condition ($\beta = -0.057, P = 0.171$). No significant between-condition differences were noted in background EMG activity ($P = 0.406$), suggesting that MEP effects were not confounded by differences in motor output.

### DISCUSSION

Here we tested whether changes in corticospinal excitability are related to learning, changes in performance (motor output), or motor error. We found increases in excitability for both low and high gains, rather than an increase and a decrease, respectively, and no increase in excitability in a performance-matched control experiment in which subjects were required to progressively ramp up motor output, suggesting that excitability changes do not directly relate to changes in performance. In addition, control experiments showed that the increases in excitability could not be attributed to correcting visual errors or changes in kinematics or EMG. Overall, the results are consistent with the idea that changes in corticospinal excitability are the result of learning rather than performance changes or errors.

Many studies have measured MEP changes after various forms of intervention with respect to motor output, including motor learning. The critical question examined here is what changes in excitability signify. Do changes in MEP amplitude relate to behavioral changes or learning, or are they merely epiphenomenal? The experimental appeal of MEPs is that they may be measured noninvasively and thus can be used in human studies. The pervasive assumption appears to be that an increase in MEP is behaviorally relevant because it should make it easier to then volitionally recruit motoneurons for execution. Interestingly, however, this assumption has been surprisingly difficult to prove. In several studies, repetitive TMS (rTMS) has been used to alter cortical excitability with inconsequential effects on motor performance (Muellbacher et al. 2000). For example, in one study subjects made repeated fast index finger abductions after 5-Hz rTMS over contralateral M1. The rTMS did not enhance motor performance on any kinematic variable compared with a sham group despite significant differences in MEPs for the two groups (Agostino et al. 2007). In another study, low-frequency rTMS over M1 reduced MEP amplitude in the FDI muscle but had no effect on maximal finger tapping speed, on performance on a grooved pegboard test, on an object grip and lift task, or on visuomotor tracking (Todd et al. 2009). Another study failed to find a relationship between increments in voluntary muscle contraction and changes in cortical excitability (Gelli et al. 2007). Conversely, however, in a study that modulated excitability with practice and ischemic nerve block, motor output was enhanced (Ziemann et al. 2001). Those few studies that arguably have shown a disruptive effect of rTMS over M1 on motor performance have related to higher-order processes rather than execution itself. For example, rTMS over M1 led to impaired grip-force scaling—subjects appeared to have disruption of their memory of the previously lifted object weight (Nowak et al. 2005). Notably, subjects generated forces larger than was required and the authors conjectured that
rTMS was disrupting sensory inputs into M1 rather than its output. This grip-force scaling effect is consistent with a more recent study that showed larger MEPs when an object that was lifted had been preceded by a heavy rather than a light object; this difference had no apparent effect on ability to scale grip-force in the subsequent lift (Loh et al. 2010). Thus review of the literature presents conflicting evidence with regard to any causal relationship between changes in corticospinal excitability and changes in motor output or performance.

Studying gain adaptation offered the ideal opportunity to dissociate performance- versus learning-related changes in excitability because low and high gains require opposite changes in motor output. For a given target in extrinsic space, after adaptation to a low gain a larger movement with a higher peak velocity is required compared with baseline, and vice versa for a high gain. If MEP amplitude reflects the magnitude of output from M1 then we should have seen opposite changes in excitability in the relevant agonist muscle at low and high gains. Instead we saw large excitability increases for both low- and high-gain adaptation and no excitability changes in a performance-matched training protocol, a result consistent with the studies cited above that showed no clear relationship between excitability and motor output (Agostino et al. 2007; Gelli et al. 2007; MueLLbacher et al. 2000; Todd et al. 2009). We conclude that excitability increases following adaptation reflect something other than altered motor output. To attribute these changes to accumulated learning, it was first necessary to control for the possibility that these changes resulted from observation of large sensory prediction errors. We found that in a pseudorandom gain condition, in which subjects had to make continuous online corrections in the setting of large errors, there was only minimal change in excitability. It therefore appears that changes in corticospinal excitability reflect accumulated learning-based modifications in a controller. Interestingly, our analysis of the pseudorandom control task revealed that the modest increases in MEPs in the low-gain condition were likely attributed to the partial adaptation that was evident in the subsequent lift (Loh et al. 2010). Thus review of the literature presents conflicting evidence with regard to any causal relationship between changes in corticospinal excitability and changes in motor output or performance.

We recently proposed that these results can be explained by positing that a second form of repetition-associated reinforcement learning occurs in adaptation paradigms and that it may occur in M1 (Huang et al. 2011). In animal models, multiple plastic changes in M1 have been described for skill learning tasks (Kleim et al. 2004; Li et al. 2001; Molina-Luna et al. 2009).

All these results in human and nonhuman animals can be unified by positing that the late reinforcement process in adaptation paradigms and skill learning are mechanistically similar, namely, that they require synaptic changes (in M1 or elsewhere) and that such changes require short-term and long-term potentiation (LTP)-like processes apparent as increases in cortical excitability (Castro-Alamancos and Connors 1997; Ziemann et al. 2004). Thus the increases in corticospinal excitability that we found here for accumulated gain adaptation are consistent with the idea that the changes in motor output required to maintain stable performance may be associated with plastic changes in the motor neuraxis, regardless of the sign of the gain change. Because excitability was assayed through changes in MEPs, it is possible that the effects observed in the present experiments represent changes at the level of M1 cell body synapses, along the length of upper motoneuron (UMN) axons, or at the level of the UMN-α-motoneuron (αMN) synapse in the spinal cord. Indeed, there is persistent debate with regard to which level of the neuraxis is the locus for such learning-dependent changes. It is known from recent magnetic resonance spectroscopy work that focal reductions in GABA inhibition occur in sensorimotor cortex during motor learning (Floyer-Lea et al. 2006), and stimulation studies have shown that the degree of learning in M1 is correlated with the ability to modulate GABA inhibition (Stagg et al. 2011), which may be artificially inhibited with stimulation techniques such as anodal tDCS (Stagg et al. 2009). Likewise, some have shown that learning has little effect on corticofugal axonal excitability (Classen et al. 1998) or spinal excitability (Kleim et al. 2002; Remple et al. 2001). Learning-related changes have been detected, however, at spinal levels, too, characterized by modulated changes in the H reflex (Meunier et al. 2007; Winkler et al. 2012; Wolpaw 2010). So far, the specific involvement of cortical versus spinal levels in motor learning remains unknown. The evidence clearly supports the notion that spinal-level reflex circuitry can be conditioned in relatively simple tasks (Thompson et al. 2009) or even by stimulation of the motor cortex (Wang et al. 2012). Empirical data suggest that voluntary acquisition of complex visuomotor skills relies on the direct involvement of motor cortex (Pruszynski et al. 2011; Pruszynski and Scott 2012). Our study was limited by the absence of spinal-level excitability measurements, limiting
our ability to isolate the precise location in the neuraxis at which our corticospinal excitability changes occurred. Regardless of the location of excitability change (M1 vs. UMN axon vs. UMN–αMN synapse) or the underlying neuronal mechanism (increased excitation vs. decreased inhibition), the present study demonstrates that visuomotor adaptation induces shorter-term, sign-independent facilitation of the corticospinal system. An interesting follow-up study would be to use the same gain adaptation paradigm (along with spinal-level assays of excitability) to test for longer-lasting effects across separate days, at varying stimulation intensities (i.e., 115% vs. 120% resting motor threshold) and background EMG levels [i.e., force output at 0 N (rest), 1 N, 3 N, etc.].

Our finding of increases in corticospinal excitability for both increases and decreases in gain is consistent with those previous studies that have shown no behavioral consequence of changes in MEP magnitude (Agostino et al. 2007; Gelli et al. 2007; Todd et al. 2009). We conclude that caution is required when reporting changes in MEP magnitude as having behavioral significance, especially in the context of neurorehabilitation. Had adaptation to the two oppositely signed gains shown a differential effect on excitability, then perhaps more of a case could have been made for using manipulations of visual feedback to enhance cortical excitability and perhaps aid voluntary recruitment. Given our results, however, we conclude that changes in corticospinal excitability are a marker for learning-related processes and should not in and of themselves be considered relevant to motor performance. That said, it is possible that if excitability is abnormally depressed, like after stroke, then methods to enhance excitability might improve performance (Hummel et al. 2005; Hummel and Cohen 2006; Khedr et al. 2005; Tanaka et al. 2009). This consideration leads to the interesting possibility that VR adaptation paradigms might indirectly benefit patients after stroke by increasing excitability, which may then enhance performance in unrelated motor tasks.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


