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Goal-directed visuomotor skill learning: Off-line enhancement and the importance of the primary motor cortex

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Abstract

Purpose: The time course and neural substrates of motor skill learning are not well-understood in healthy or neurologic patient populations. Certain motor skills undergo off-line skill enhancement following training and the primary motor cortex (M1) may be involved. It is unknown if goal-directed visuomotor skill undergoes off-line enhancement or if M1 is associated with that enhancement.

Methods: 32 right-handed, healthy subjects were randomly assigned to two groups: real repetitive transcranial magnetic stimulation (rTMS) or sham rTMS applied to the contralateral M1 immediately following one 20-minute finger tracking training session. Tracking performance and cortical excitability were assessed before and after training, following rTMS and 24 hours post-training.

Results: Results demonstrate that skill performance continues to develop for at least 30 minutes after training completion, is maintained for 24 hours post-training, and is not affected by inhibitory rTMS applied to M1. Level of skill improvement was associated with the degree of intracortical inhibition increase.

Conclusions: These results suggest dispersed information processing for goal-directed visuomotor skill learning following training and a relationship between cortical excitability and skill development in healthy individuals. These findings invite further investigation of the neural mechanisms underlying motor skill learning and may have rehabilitation implications for patients with neurologic injury.

Keywords

Motor skill; learning; memory; rTMS; enhancement; primary motor cortex

1. Introduction

Motor skill learning involves a collection of neural processes in response to experience or practice that, over time, lead to lasting changes in the capacity for producing a specific skilled action. When a novel skill is presented, rapid improvements in performance can be

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observed, reflecting short-term changes in neuronal excitability and connectivity (Ziemann, 2004; Sun et al., 2007). These initial skill improvements result from novel information acquisition and require further processing following exposure to allow for future retrieval. Consolidation of this information is evidenced by a decreased susceptibility to interference and subsequent retention of previous learning when the skill is later performed (Sanes and Donoghue, 2000; Krakauer and Shadmehr, 2006). This off-line consolidation process may consist of stabilization or even enhancement of an acquired motor skill memory (Walker, 2005). The time course and neural substrates of these processes are not well understood in healthy or neurologic patient populations.

Substantial behavioral and neurophysiologic data exist for motor sequence and dynamic adaptation learning [for review: (Ashe et al., 2006; Krakauer and Shadmehr, 2006)], but considerably less is known about the stages of memory formation and neural processes involved in goal-directed, continuous, visuomotor skill learning. This type of learning has been well studied in investigations of motor impairment and in the evaluation of rehabilitation outcomes (DeSousa, 1980; Halaney and Carey, 1989; Bate and Matyas, 1992; Kimberley et al. 2008), particularly through the use of a continuous visuospatial finger tracking task. Visually-guided finger-tracking training has been shown to be associated with cortical reorganization in multiple brain regions in conjunction with motor performance improvements in both healthy subjects and stroke patients (Carey et al., 2002; Kimberley et al., 2004; Bhatt et al., 2007). To this point, immediate post-training memory processing and the neural substrates required for this type of skill learning, shown to be sensitive to motor impairment and motor recovery following neurologic insult, have not been determined.

Previous research has demonstrated that primary motor cortex (M1) activity is altered when exposed to novel motor skill training (Karni et al., 1995; Classen et al., 1998). This region also plays a role in initial motor skill acquisition (Kobayashi et al., 2009) as well as during off-line information processing (Muellbacher et al., 2002; Robertson et al., 2005). Transcranial magnetic stimulation (TMS) has been utilized as a non-invasive strategy to evaluate and quantify the cortical activity changes associated with motor learning. In addition, when TMS is applied repetitively (rTMS), cortical activity can be transiently disrupted, allowing investigation of structure-function relationships between brain regions and behavior (Robertson et al., 2003). This technique has demonstrated a role for M1 in the immediate post-training consolidation of simple ballistic skills (Muellbacher et al., 2002; Baraduc et al., 2004), but not for consolidation of force field adaptation during reaching (Baraduc et al., 2004). It has also been shown to disrupt immediate skill acquisition for visuomotor finger tracking skill when rTMS was applied prior to training to the M1 ipsilateral to the trained hand but not when applied to the contralateral M1 (Carey et al., 2006). The effect of rTMS-induced disruption of the contralateral M1 activity following finger-tracking training has yet to be investigated.

Currently, there remains a paucity of data regarding post-training memory formation of, and the neural substrates involved in, explicitly-acquired, goal-directed, visuomotor skill learning in both healthy and patient populations. Therefore, the primary purpose of this study was to determine if finger-tracking skill undergoes off-line enhancement following training and if the improvements were maintained for at least one day in healthy individuals.

A secondary purpose was to determine if rTMS-induced disruption of M1 immediately following training attenuates skill performance. Thirdly, the relationship between skill performance and M1 excitability was explored.

2. Materials/methods

2.1 Research design/ethics statement

A pseudo-randomized, single-blind, sham controlled study design (Fig. 1A) was used. Subjects were recruited from a sample of convenience through postings on the University of Minnesota campus. Thirty-two right-handed, [>70 on Edinburgh Handedness Inventory (Oldfield, 1971; Dragovic, 2004)] healthy subjects ($25.97 \pm 3.8y$, 17F) were assigned to one of two stimulation groups (real rTMS or sham rTMS). Exclusion criteria were: (1) any diagnosed neurologic condition, (2) orthopaedic injury to the upper extremity, (3) seizure history, (4) pregnancy, (5) metal in head, or (6) implanted medical devices (Wassermann, 1998). Subjects were not screened regarding any visuomotor skill performance proficiencies. The study was approved by the University of Minnesota General Clinical Research Center and Institutional Review Board and subjects provided informed written consent in accordance with the Declaration of Helsinki prior to participating.

2.2. Visuomotor skill assessment

Subjects were initially assessed on a novel finger tracking task that involved flexion and extension movements of the right index finger to control a cursor along the y -axis while it moved independently across the x -axis from left to right on a computer screen at a fixed frequency (0.6 Hz). The goal of the task was to trace the computer-generated target waveform as accurately as possible. Movement was recorded by a potentiometer affixed to a splint parallel to the metacarpophalangeal (MP) joint of the index finger (Fig. 1B). Subjects were verbally instructed on the goal and constraints of the task and had their finger passively moved during one trial and then performed one active practice trial to allow for task familiarization and to demonstrate understanding of the task requirements. Each finger tracking skill assessment (FT) consisted of five 10-second tracking trials of a sawtooth waveform separated by a 1-second rest period (Fig. 1C). To assess skill improvement, assessments were made prior to training, immediately following training, 5- and 15-minutes post-rTMS stimulation, and at 24-hour follow-up. Performance was quantified by an accuracy index (AI): $100(P-E)/P$, where P is the magnitude of the subject's target pattern and E is the root-mean square error between target line and response line (Carey, 1990; Carey et al., 1998). The AI is a composite measure of the spatial and temporal aspects of skill performance. This measure has been previously validated in healthy and stroke populations (Carey, 1990; Carey et al., 1998).

2.3. Visuomotor skill training

The same tracking apparatus and positioning used for assessments was used for the 20-minute finger tracking training session. This training consisted of 105 trials presented consecutively during the session. Knowledge of performance was provided in real time by the cursor trace produced during each trial and knowledge of results was provided in the form of an AI score. Feedback was faded as training progressed. A host of training

protocols, created by varying tracking conditions and target parameters, were used to introduce variability and promote greater depth of cognitive processing. These variations included: altering peak-to-peak amplitude of finger movement (0–100% of individual ROM), varying cursor speed (0.2–1.0Hz), adjusting trial length (5–20 seconds) changing the target waveform (sine, cosine, triangle, square, random), reversing potentiometer polarity to introduce stimulus-response incompatibility (MP extension results in downward cursor movement and upward for MP flexion) and modifying forearm position (full pronation or neutral). To ensure transfer of the tracking skill, the waveform employed during the skill assessments described above was not repeated in the training protocol.

2.4. Cortical excitability assessment

Resting motor threshold (RMT) for TMS activation of the right first dorsal interosseous (FDI) muscle was determined prior to pre-training motor skill assessment using previously described methods and equipment [70-mm figure-eight TMS coil connected to a Magstim 200² monophasic stimulator (Magstim Co. LTD, Whitland, UK)] (Rossini et al., 1999). Using this value, cortical excitability (CE) was assessed utilizing the measures outlined below. These measures were repeated at the same intervals as the skill assessments: pre-training, post-training, 5- and 15-minutes post-stimulation and at 24-hour follow-up.

Measures of CE were assessed by single-pulse (120% RMT) motor evoked potential (MEP) amplitude and paired pulse short-interval intracortical inhibition (SICI). Single-pulse MEP amplitude is thought to be a measure of overall corticospinal excitability (Wassermann, 2008). During SICI assessment, a subthreshold (90% RMT) conditioning pulse was delivered at a short (3 ms) latency prior to a suprathreshold (120% RMT) test pulse (Kujirai et al., 1993). The change in MEP amplitude due to conditioning pulse latency was measured and is believed to represent primarily γ -aminobutyric acid_A-mediated local intracortical inhibitory processes (Ziemann et al., 1996). Paired TMS stimuli were delivered with two Magstim 200 devices connected through a Magstim BiStim² Module over the previously identified location of FDI activation while the hand was at rest. For each trial ($n = 10$) within each assessment, paired pulse amplitudes were normalized to the mean single-pulse MEP ($n = 10$) for that assessment (Maeda et al., 2002).

2.5. rTMS procedure

Immediately following the motor training session, post-training CE and behavioral assessment, subjects received one 10-minute bout of rTMS (90% RMT) at 1 Hz to the region of M1 previously identified to optimally activate the contralateral FDI. These parameters have previously been shown to alter cortical excitability and behavior (Robertson et al., 2003, 2005; Carey et al., 2006). The sham rTMS protocol exactly mimicked the real rTMS protocol, except the coil was orthogonally positioned to discharge each pulse away from the scalp preventing current delivery to the cortex (Lisanby et al. 2001; Muellbacher et al., 2002).

2.6. Statistical analysis

All data were assessed for normality and heterogeneity of variance. If the data violated the assumptions of parametric analysis, data were then log-transformed and reassessed.

Accuracy index (AI) and measures of cortical excitability (single-pulse MEP, paired-pulse SICI) were analyzed using repeated measures three-way ANOVAs with group (real vs. sham stimulation) as the between-subjects factor and assessment (pre-training vs. post-training vs. post-stimulation 5 min, 15 min vs. follow-up) and trial as the within-group factors. Mauchly's test was used to assess sphericity. If sphericity was violated, Geisser-Greenhouse correction was applied. Regression analyses were conducted using AI as the response variable and single-pulse MEP and SICI as predictor variables for each assessment. A critical alpha level was set at $p < 0.05$ and effect sizes were determined for significant results using Cohen's d . Two-tailed post-hoc t -tests for paired samples with Bonferroni correction for multiple comparisons were conducted as appropriate. Simple effects analyses were performed for significant interaction effects (Howell, 2007).

3. Results

3.1. Tracking performance

Repeated-measures ANOVAs revealed significant main effects of assessment ($F(4,30) = 62.99$, $p < 0.001$) and tracking trial ($F(4,30) = 18.70$, $p < 0.001$) for AI. Post-hoc analyses demonstrated differences in AI between baseline assessment and all subsequent assessments ($d = 0.74$ – 1.62) and between post-training assessment and both post-rTMS assessments and at 24 hr follow-up ($d = 0.60$ – 1.09) (Fig. 2A). There was no significant effect of rTMS group or an interaction effect between rTMS group and assessment (Fig. 2A). Order effect of within-assessment trials was assessed and significant increases in AI were found for the last three trials of an assessment compared with the first two trials ($d = 0.25$) (Fig. 2B). An interaction effect between assessment and trial was also observed ($F(16,30) = 4.45$, $p < 0.001$). Simple effects analyses demonstrated the interaction effect between assessment and trial was due to a significant increase in AI between trials in both pre- and post-training assessments but no increase in AI across trials for subsequent assessments was observed ($d = 1.45$) (Fig. 2B).

3.2. Cortical excitability

No difference in cortical excitability was observed between stimulation groups at any assessment. A significant main effect of assessment was observed for single-pulse MEP amplitude ($F(4,30) = 3.26$, $p = 0.01$) (Fig. 3). Post-hoc analyses revealed significant decreases in MEP amplitude at the post-training assessment compared to pre-training ($d = 0.10$), post-rTMS ($d = 0.36$) and follow-up ($d = 0.16$) assessments. A trend for a main effect of assessment was also observed for paired-pulse SICI MEP ratios ($F(4,40) = 2.44$, $p = 0.05$). Post-hoc testing revealed an increase in SICI immediately following rTMS ($d = 0.29$) compared to SICI after training.

Regression analyses were conducted using the change in AI from pre-training assessment to 24-hour follow-up assessment as the response variable while changes in single-pulse MEP amplitude and SICI MEP ratios between the two assessments were evaluated as predictor variables. These measures were chosen a priori based on pilot data results to investigate the within-subject relationships between behavioral performance and cortical excitability. A significant relationship between AI and single-pulse MEP was not observed. A significant

positive relationship between AI change and SICI MEP ratios change was found ($r^2 = 0.27$, $p = 0.002$) (Fig. 4).

4. Discussion

This study investigated the time course of a novel, goal directed visuomotor skill learning and the influence of M1 immediately following one training session in healthy individuals. All subjects, regardless of the type of stimulation received, demonstrated off-line performance enhancement within thirty minutes following training that remained stable for at least 24 hours. This enhancement was not attenuated by transient disruption of the contralateral M1 by inhibitory rTMS after training. Additionally, the magnitude of skill improvement was associated with the level of increase in intracortical inhibition from pre-training to one-day follow-up assessment. These are the first findings demonstrating off-line memory enhancement for an explicitly-acquired, goal-directed visuomotor skill in conjunction with a relationship between skill development and intracortical excitability in healthy subjects.

Motor skills are comprised of multiple components that are dedicated to specific neural circuits (Hikosaka et al., 1998, 2002; Cohen and Robertson, 2007). Motor skills may develop after practice has ended during a critical period of off-line memory consolidation. It has been shown previously that certain tasks undergo off-line skill enhancement and that there may be different critical time periods and brain states for these processes to occur that depend on the features of the task and training paradigm (Cohen et al., 2005; Robertson et al., 2005; Hotermans et al., 2008). This work demonstrates that goal-directed, continuous visuospatial skill information that is explicitly-acquired during a single training period undergoes post-training enhancement and rTMS aimed at disrupting normal contralateral M1 activity following training does not attenuate this performance improvement.

Low-frequency rTMS applied to M1 immediately following training of a ballistic motor skill but not a dynamic adaptation task has been shown to reduce skill retention (Muellbacher et al., 2002; Baraduc et al., 2004). It has been postulated that differences in task requirements will result in differential activation of brain regions across the time course of memory formation (Walker, 2005). As task complexity increases, there is a greater likelihood for parallel information processing to occur in multiple brain regions simultaneously (Robertson et al., 2005). In the present study, inhibitory rTMS applied to M1 did not affect immediate or delayed skill retention, suggesting that immediately following training of a goal-directed visuomotor skill, M1 may not be principally involved in off-line enhancement of all motor skills.

Interpretation of the role of M1 in this task is limited by the lack of significant cortical excitability changes observed following rTMS between groups. Our results did demonstrate a significant increase in intracortical inhibition following rTMS compared to immediately after training but a significant difference between real and stimulation groups was not observed. In our study, a subthreshold stimulus intensity was chosen to minimize stimulus spread to adjacent brain regions, such as dorsal premotor or supplementary motor cortices, and to avoid potential peripheral influences of repeated FDI activation on cortical activity

(Fitzgerald et al., 2002). This chosen intensity and/or duration of application may have been insufficient in producing substantial disruption of M1 activity observed in similar experimental paradigms utilizing longer durations of suprathreshold rTMS (Muellbacher et al., 2002; Baraduc et al., 2004). We find this unlikely, however, as the stimulation parameters for this study have previously been shown to block off-line learning following training, although, measures of cortical excitability were not reported, therefore it is unknown if there were concomitant cortical excitability changes (Robertson et al., 2005). However, it is important to note a lack of effect on skill development does not provide proof that M1 is not involved during immediate post-training processing of a goal-directed visuomotor skill (Reis et al., 2008).

Additionally, the relatively small number of trials collected for SP and SICI measurement may have obscured potential group differences since it has been shown previously that the number of trials collected has a substantial impact on the reliability of cortical excitability measures (Schmidt et al., 2009). Retrospective power analyses indicate 76 subjects per group would be sufficient to demonstrate population effects of rTMS-induced disruption on contralateral M1 excitability. Future studies could modify stimulation intensity, length of stimulation or stimulation type to determine optimal stimulation parameters to induce maximal transient disruption of cortical activity. Additionally, increasing the number of stimuli collected may reduce variability in cortical excitability measurement depending on the time constraints of the experimental paradigm.

Previous literature investigating the neural substrates of behavior has been unsuccessful in demonstrating a consistent relationship between cortical excitability and skill performance. Our results suggest that increases in intracortical inhibition are associated with increases in finger tracking accuracy between pre-training and 24-hour follow-up assessments. Potentially, there may be multiple explanations for this finding. It may be that M1 is differentially recruited based on the amount and time of exposure of this skill. It has been shown using fMRI that neural activity in cortical regions, including contralateral M1, decreases following short-term visuomotor learning (Floyer-Lea and Matthews, 2004). Interestingly, it appears that this dynamic shift in cortical activation can occur rapidly or gradually depending on the type of motor skill trained and the relative degree to which has been learned over time (Koenke et al., 2006). These results support a dynamic nature of brain activation patterns shifting from widely-distributed cortical activation during early performance and learning to subcortical activation once the task has been learned and largely automated. This may occur across different time periods depending on the skill learned and the training paradigm (Floyer-Lea and Matthews, 2004; Koenke et al., 2006).

It appears that early motor skill performance requires substantial neural resources responsible for sensorimotor integration, motor planning, and executive functioning to accomplish a skill successfully but once learned, efficient neural processing is then associated with successful performance (Walker et al., 2005; Orban et al., 2010). Although dynamic changes in regional brain activity were not monitored here, it has been shown previously that regional reductions in brain activity were associated with local reductions in cortical excitability (Hummel et al., 2004). Therefore, dynamic changes in brain activity patterns from predominately cortical, prior to training, to subcortical, once the skill is

learned and automated, may explain the observed association of greater improvement in finger tracking accuracy in response to training with greater changes in intracortical inhibition.

5. Conclusions

We have shown that goal-directed visuomotor skill continues to develop following training in the absence of further practice and remains stable for at least one day after training completion in healthy individuals. Also, a stimulation protocol aimed at disrupting M1 activity immediately after training did not affect skill enhancement, suggestive of parallel and/or distributed information processing during this time period. Interestingly, the magnitude of skill improvement in response to training was associated with the level of increase in intracortical inhibition from pre-training to 24-hour follow-up assessment.

These results may have implications for rehabilitation following neurologic injury. Understanding the role of specific cortical areas during motor skill development may help therapists to optimize rehabilitation outcomes by targeting specific brain regions at specific stages of motor skill learning.

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Fig. 1.
A) Schematic of study design. B) Finger tracking apparatus with assessment waveform displayed on computer screen. C) Representative tracking response from one subject.

Fig. 2.

A) Tracking performance (AI $\pm$ SE) comparison between groups and across assessments. No significant difference between stimulation groups was observed. When collapsed across group, there were significant improvements in AI after training ($*p < 0.001$) that continued without further training and were maintained for at least 24 hours following training ($**p < 0.001$). B) A trial by assessment interaction was detected across subjects regardless of stimulation group. Significant increases in AI were seen across trials (1–2 vs. 3–5, $***p =$

0.05) in pre- and post-training assessments but no increases in AI were found for post-rTMS assessments or at follow-up.

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Fig. 3.

Left: Single-pulse MEP amplitudes were reduced ($*p = 0.005$) following training compared to pre-training, 5-minutes post-rTMS and 24-hour follow-up. Right: After rTMS, SICI MEP ratios were decreased ($*p = 0.005$) regardless of level of stimulation.

Fig. 4.

The relationship between the change in AI and SICI MEP ratios between pre-training and 24-hour follow-up assessments was significant ($r^2 = 0.27$, $p = 0.002$). Greater changes in tracking performance were associated with greater increases in intracortical inhibition.