Published in final edited form as:

Exp Brain Res. 2011 October ; 214(4): 619–630. doi:10.1007/s00221-011-2863-0.

Both sleep and wakefulness support consolidation of continuous, goal-directed, visuomotor skill

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Abstract

Sleep has been shown to benefit memory consolidation for certain motor skills, but it remains unclear if this relationship exists for motor skills with direct rehabilitation applications. We aimed to determine the neurobehavioral relationship between finger-tracking skill development and sleep following skill training in young, healthy subjects. Forty subjects received tracking training in the morning ($n = 20$) or the evening ($n = 20$). Measures of tracking skill and cortical excitability were collected before and after training. Following training, tracking skill and measures of cortical excitability were assessed at two additional follow-up visits (12 and 24 h post-training) for each subject following an episode of sleep or waking activity. Two-way repeated-measures ANOVAs with Bonferroni-adjusted post hoc tests were conducted for tracking accuracy and measures of cortical excitability. Skill performance improved after training and continued to develop offline during the first post-training interval (12 h). This development was not further enhanced by sleep during this interval. Level of skill improvement was maintained for at least one day in both training groups. Cortical excitability was reduced following training and was related to level of skill performance at follow-up assessment. These data suggest offline memory consolidation of a continuous, visuospatial, finger-tracking skill is not dependent on sleep. These findings are in agreement with recent literature, indicating characteristics of a motor skill may be sensitive to the beneficial effect of sleep on post-training information processing.

Keywords

Sleep; Motor learning; Transcranial magnetic stimulation; Excitability; Primary motor cortex; Memory consolidation

Background

A considerable body of literature has supported a beneficial role of sleep in implicit sequence skill learning and enhanced memory consolidation (Walker et al. 2002, 2003b; Kuriyama et al. 2004). Consolidation is the neural processing of newly acquired information resulting in retention over time and resistance to interference. In some cases, the information is not only retained following acquisition but may also continue to develop, resulting in enhanced skill performance at retention testing (Robertson et al. 2004, 2005; Cohen et al. 2005).

Motor skills are comprised of multiple components dedicated to specific neural circuits that may be differentially affected by skill training paradigms and post-training activity (Hikosaka et al. 1998, 2002; Cohen and Robertson 2007). Explicit awareness of motor skill acquisition has demonstrated sleep-dependent performance gains that are not observed solely with the passage of time (Robertson et al. 2004). It also appears that sleep preferentially benefits goal-directed (Cohen et al. 2005) and complex motor skill learning (Kuriyama et al. 2004). Cohen et al. (2005) showed that movement-based motor sequencing skill improvement occurs only during a waking interval, while goal-based sequence skill enhancement requires sleep following training (Cohen et al. 2005; Cohen and Robertson 2007). Relatedly, performance on a dynamic force field adaptation task was compared to an explicit version of a four-element serial reaction time task (SRTT) after an interval consisting of waking activity or one interval containing sleep (Doyon et al. 2009). Results indicated that SRTT performance was enhanced following sleep, while adaptation performance was improved with the simple passage of time (Doyon et al. 2009). These findings contrast previous sequencing and adaptation results by showing that not all motor tasks undergo sleep-dependent enhancement (Goedert et al. 2002; Tucker et al. 2006) but may support a preferential role for sleep in enhancing the consolidation of explicit information associated with a given motor skill.

Previous work using various neuroimaging approaches has demonstrated involvement of the contralateral primary motor cortex (M1) in skill acquisition and post-training memory consolidation (Karni et al. 1995; Muellbacher et al. 2001; Hotermans et al. 2008). A number of studies have shown substantial changes in cortical representation following skill training that are specific to the trained cortical representation in M1 (Classen et al. 1998; Muellbacher et al. 2001; Huber et al. 2004). Specifically, transcranial magnetic stimulation (TMS) can probe relationships between local brain activity and motor skill performance. Using TMS, increases in M1 excitability immediately following different skill training paradigms have been observed (Muellbacher et al. 2001; Gallasch et al. 2009). In contrast, following visuomotor tracking training, M1 excitability was decreased (Borich et al. 2011). Importantly, these changes in excitability are transient and appear to occur early during the skill acquisition phase of motor learning (Ziemann et al. 2001, 2004; Floyer-Lea and Matthews 2004). The relationship between cortical excitability and motor skill development remains largely unknown.

Sleep has been shown to benefit consolidation of certain motor skills that have been recently acquired, but it remains unclear whether this benefit also applies to explicit, continuous,

goal-directed motor skills that have direct applications to rehabilitation (Carey et al. 2002; Kimberley et al. 2004). Additionally, despite the intensity of inquiry into the relationship between sleep and motor learning, the associated neural mechanisms are not well characterized. Thus, purpose of this investigation was to: (1) evaluate the role of sleep in the time course of novel visuospatial motor skill learning and (2) examine the neural processes underlying this learning.

Methods

Experimental design

A single-blind, pseudo-randomized design was employed, whereby forty right-handed healthy subjects were assigned to either: (1) day skill training (age: 23.2 ± 3.9 years, 10F) or (2) night skill training (age: 21.9 ± 3.8 years, 10F). All subjects were recruited through the use of University and local community advertisement. Standard exclusion criteria for TMS were used (Rossi et al. 2009). At the initial visit, all subjects gave written and informed consent according to the Declaration of Helsinki. Handedness was determined by the Edinburgh Handedness Inventory (EHI) (Oldfield 1971). Subjects completed finger-tracking (FT) and cortical excitability (CE) assessments prior to, and following, one twenty-minute skilled finger-tracking training session. All subjects participated in three visits, each separated by 12 h, where the initial visit occurred either in the morning (8 am) or evening (8 pm) depending on group assignment. After the first 12-h interval consisting of normal waking activity or an interval containing sleep, each subject returned for follow-up assessments of FT and CE without further training exposure. After another 12-h interval containing sleep or waking activity, subjects returned for a second follow-up assessment, 24 h after training (Fig. 1a). All subjects kept a sleep diary for the nights before and during participation to subjectively monitor sleep. Wrist actigraphy was performed the night prior to training and the night after training to objectively measure sleep quality (Sadeh et al. 1994; Morgenthaler et al. 2007).

TMS targeting of M1 and cortical excitability assessment

While seated, subjects wore a tight-fitting Lycra swimming cap to mark the optimal scalp position for stimulation. Earplugs were worn by the subjects to prevent auditory threshold shifts and minimize stimulation-associated noise. Silver/silver chloride disposable electrodes were affixed in a belly-tendon montage of the right first dorsal interosseous muscle (FDI). To determine resting and 1 mV motor thresholds (rMT and 1 mVT), the arm was placed in a relaxed, comfortable position to minimize muscle activation in the limb. Alligator clip lead wires were attached to each electrode and connected to a Cadwell Sierra amplifier (Cadwell Laboratory, Washington) (sensitivity: 100 μ V/div, filter: 20–2,000 Hz). Electromyographic (EMG) signals were acquired at a sampling rate of 2,560 kHz for 100 ms, with a 10-ms pre-stimulus epoch to monitor pre-stimulation activation to ensure the muscle remained at rest. For active motor threshold (aMT) determination, subjects were asked to actively abduct the second digit (5–10% of maximum voluntary contraction of FDI (Rosler et al. 2002) against a strain gauge coupled to a load cell. Continuous visual feedback of contraction level was provided on a computer display in front of the subject.

To find the optimal position for activating the FDI, a 70-mm figure-eight TMS coil connected to a Magstim rapid magnetic stimulator (Magstim Co Ltd. Dyfed, UK) was used. The coil was held tangentially to the skull with the handle directed 45° posterolateral to the midsagittal line of the skull producing a posterior-anterior current flow in the brain (Sakai et al. 1997). Single-pulse magnetic stimuli were delivered to the scalp location overlying the presupposed M1 locus for optimal FDI activation at approximately 0.1 Hz starting at an intensity of 50% of the maximum stimulator output (MSO). For rMT determination, level of intensity was adjusted systematically until the rMT was found, defined as the minimum intensity required to elicit MEPs > 50 μ V peak-to-peak in at least 5 of 10 trials of FDI at rest (Rossini et al. 1999). Once intensity was identified, the location of coil was moved 1 cm anteriorly, posteriorly, medially and laterally to assess responsiveness of neighboring regions to stimulation. The locus for subsequent TMS procedure was determined by the location demonstrating the lowest rMT. This location was then used to determine intensity level of aMT and 1mVT. The same procedure was used for aMT determination except the MEP response threshold had to exceed 200 μ V peak-to-peak in at least 5 of 10 trials (Rossini et al. 1999). For 1 mVT, stimulus intensity was varied until MEPs of ~ 1 mV were consistently evoked (Sanger et al. 2001). Using these identified intensities, measures of cortical excitability were then collected.

Four primary measures of cortical excitability were collected: (1) single-pulse (SP) MEPs, (2) paired-pulse (PP) MEP ratios (3/10 ms), (3) cortical silent period duration (CSP) (ms) and (4) motor threshold stimulation intensity (rMT, aMT, 1mVT) (% MSO) (Fig. 1b). Twenty SP MEP trials were collected (gain: 500 μ V/div, filter: 20–200 Hz, sweep interval: 10 ms/division) using a 1 mVT test pulse. Paired-pulse MEPs were collected to assess short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF), where a subthreshold (90% aMT) conditioning pulse was delivered at a short (3 ms) or long (10 ms) interstimulus interval prior to 1 mVT test pulse delivery (Kujirai et al. 1993; Ziemann et al. 1996c). Paired TMS stimuli were delivered with two Magstim 200 devices connected through a Magstim BiStim² Module (Magstim Co LTD, Whitland, UK) through a standard 70-mm coil over the previously identified location of FDI activation while the hand was at rest. Ten trials were collected for each ISI alternating between ISIs every two trials to minimize priming effects. Peak-to-peak amplitudes were identified offline for each MEP collected. Data were then indexed to the mean SP MEP amplitude ($n = 20$ trials) for the same assessment session (PP MEP / SP MEP_x) (Maeda et al. 2002).

To determine CSP duration, subjects performed a sustained abduction force (20% maximum voluntary contraction) of the index finger against a strain gauge coupled to a load cell. Force output was transduced and displayed on a computer screen placed in front of the subject. Subjects were asked to maintain this contraction for 6 s while a single test pulse (150% aMT) was administered. Trials were collected every 20 s to prevent fatigue and summative effects of the stimulation. To determine CSP onset, the first superimposed TMS-induced EMG peak was identified. The CSP offset was defined as the resumption of sustained volitional EMG activity that surpassed 50% of the average pre-stimulus EMG activity (25 ms) (Kimberley et al. 2009). This TMS targeting and cortical excitability procedure was

conducted in the same manner during each of the four assessments (pre-training, post-training, 12-h follow-up and 24-h follow-up).

Visuospatial motor skill assessment

To investigate motor skill performance, subjects were tested on a novel finger-tracking task involving flexion and extension movements of the right index finger. A custom-made electrogoniometer, consisting of a potentiometer attached to a splint, was used (Carey et al. 1994). When donned, the potentiometer was centered at the index finger metacarpophalangeal (MP) joint to measure change in joint position during active movement. The forearm was placed in a pronated position for testing and supported while allowing full index finger range of motion (ROM). In addition, the shoulder was allowed to rest comfortably at the side with the elbow at $\sim 90^\circ$ of flexion.

Active movements involved tracking of a computer-generated target waveform moving independently at a fixed frequency from left to right on a computer display in front of the subject. After affixing the splint, subjects were verbally instructed on the goal of the tracking task as well as the dynamics of the task. Then, their finger was passively moved during one 5-s practice trial. During another 5-s trial, subjects actively tracked the target to ensure task familiarization while preserving task novelty.

During each finger-tracking (FT) assessment, there were ten consecutive 10-s tracking trials presented. Half of the trials were stimulus–response (S–R) compatible, and the other five were incompatible. In the compatible condition, the cursor moved in the same direction as finger movement, while in the incompatible condition, the cursor moved in the opposite direction of finger movement. These two conditions were randomly presented during each FT assessment. The test waveform was a triangle wave with a peak-to-peak amplitude of 15–85% of each subject's full, comfortable ROM. The tracking cursor moved at a fixed frequency of 0.6 Hz. Motor skill performance was quantified using an accuracy index (AI): $AI = 100(P - E)/P$, where E is the root-mean-square error between the target line and the performance line and P is the size of the target pattern defined as the root-mean-square difference between the wave and the midline separating the wave (Carey et al. 2002). This accuracy value accounts for inter-subject differences in finger ROM to determine individual tracking performance and compare across subjects. Skill assessments were performed immediately before and after training during the initial visit and at both follow-up visits.

Visuospatial motor skill training

The same tracking apparatus and positioning were utilized for the 20-min motor skill training session. This training consisted of 105 trials separated into four 5-min training blocks with 1-min rest periods between each block to minimize fatigue and promote optimal effort and motivation. Knowledge of performance was provided visually by a cursor trace produced during each trial, but no feedback was given by the examiner to control for potential differences in feedback quantity and/or quality. Knowledge of results (KR) was provided every fifth trial in the form of an accuracy score displayed after trial completion for 1 s during the first two training blocks. In the third and fourth blocks, KR was faded and

provided every tenth trial. For each 5-min training block, there were 27–30 trials with a 1-s rest in between each trial.

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), frequency (0.2–1.0 Hz), adjusting trial length (5–20 s), changing the target waveform shape (sine, cosine, saw-tooth, square, random), reversing potentiometer polarity to introduce stimulus–response incompatibility (Carey et al. 1995) and modifying forearm position (full pronation or neutral). The task parameters employed during the skill assessments were not repeated in the training protocol to avoid practice-related improvements on the test waveform outside skill assessments. This training paradigm was identical for all subjects.

Actigraphic sleep assessment

Subjects were provided an actigraphy monitor (ActiSleep sleep monitor, ActiGraph™, Pensacola, FL) the day before the initial visit. Subjects were instructed to wear the monitor on their dominant wrist during time in bed the night preceding training and the night following training to objectively assess sleep quality (Morgenthaler et al. 2007). Movement data were collected, summated over 60-s epochs and converted to digital activity counts at 60 Hz. Sleep scoring was conducted using the ActiLife software package (v. 4.4.1, ActiGraph™, Pensacola, FL). An adapted scoring algorithm was used to determine the sleep state for each recorded epoch across a sliding 11-min window (Sadeh et al. 1994). Sleep diary entry was used to determine time into and out of bed. Measures of sleep quality are summarized in Fig. 1b.

Level of arousal and sleep characteristics

Self-reported measures of sleepiness and sleep quality were collected using the Stanford Sleepiness Scale (SSS) (Hoddes et al. 1973) Pittsburgh Sleep Quality Index (PSQI) (Buysse et al. 1989) and Epworth Sleepiness Scale (ESS) (Johns 1991). The SSS was administered at the beginning and end of the first session and at the beginning of each follow-up session. The PSQI and ESS were administered to subjects at the beginning of the first visit.

Statistical analyses

Normality and heterogeneity of variance were assessed for each dependent measure. If violations were observed, log transform was attempted (Portney and Watkins 2000). Differences in subject characteristics (age, handedness, PSQI, ESS and SSS) between groups were evaluated using independent samples *t* tests (critical α -level: $P = 0.05$). Baseline differences in skill performance and cortical excitability were also assessed to determine whether initial level of performance or excitability should be added to subsequent analysis steps as a covariate.

First, univariate ANOVAs were conducted to assess for trial effects for measures involving multiple trials of each collected during an assessment (mean AI collapsed across S–R compatibility conditions, measures of cortical excitability). Data were subsequently grouped

based on these results, and trials were averaged across each assessment for the next stages of statistical analysis.

Repeated-measures two-way (group $\times$ assessment) ANOVAs were conducted for motor skill performance (AI) and cortical excitability measures. Repeated-measures ANOVAs were also conducted for actigraphy measures with main effects of night (night before initial visit and night following training) and training group. Mauchly's test was used to determine whether sphericity was violated and, if violated, Greenhouse-Geisser adjustments to degrees of freedom were applied. Partial η^2 was calculated to determine the effect size of significant results. Two-tailed post hoc pairwise comparisons with Bonferroni correction for multiple comparisons were conducted for significant results.

Regression and correlational analyses were conducted to evaluate associations between tracking performance and cortical excitability. Hierarchical multiple regression analyses were used to evaluate the predictive capacity of cortical excitability for tracking performance at each assessment. For each regression analysis, correlations between predictors and dependent measures were conducted first. Using these results, order of entry in the model was determined. Zero-order, part and partial correlations were produced for each model. Colinearity between multiple predictors was evaluated using variance inflation factor (VIF) and tolerance levels. The values under 10 for VIF and above 0.1 for tolerance were critical levels for acceptable colinearity (Field 2009). Residual statistics and plots were produced to ensure normality and heteroscedasticity of the data (Howell 2007; Field 2009). Durbin-Watson diagnostics were provided to ensure independence of the residuals from the regression analysis. Casewise diagnostics were used to determine extreme outliers in the model ($>3SD$) (Field 2009). Identified cases ($n < 3$ for all analyses) were removed and the regression analysis was run again. The final model for each analysis was based on overall significance of each model (critical α -level: $P = 0.05$), and the significance level of the R^2 changes when adding a new predictor to the model.

Results

Subject characteristics

Data were normally distributed, and homogeneity of variance was confirmed for subject characteristics. There were no statistically significant differences for age, handedness, subjective sleep quality or sleepiness between day and night training groups (Fig. 1c).

Finger-tracking performance

Accuracy index data were not found to violate the assumptions of normality. A trial effect was observed [$F(4,1,490) = 20.96$, $P < 0.001$, partial $\eta^2 = 0.04$]. Pairwise comparisons for trial indicated that trial 1 was significantly different than the other 4 trials (mean AI difference $\pm$ SE: $8.7 \pm 1.4\%$, $P < 0.005$). For the trial-by-assessment interaction, simple effects analyses indicated that trial 1 AI scores were lower than all other trials at pre-training (mean AI difference $\pm$ SE: $23.8 \pm 2.0\%$, $P < 0.05$). At 12-h follow-up, trial 1 AI scores were lower than trials 3–5 (mean AI difference $\pm$ SE: $6.3 \pm 1.9\%$, $P < 0.05$). No differences between trials were noted at post-training or 24-h follow-up. Trial 1 was subsequently

evaluated separately from trials 2–5. For assessment of trial 1 only, RM ANOVAs revealed a significant main effect of assessment [$F(1.77, 61.84) = 67.70, P < 0.001$, partial $\eta^2 = 0.66$]. For both training groups, pre-training AI scores were lower than the other three assessments (mean AI difference $\pm$ SE: $31.2 \pm 3.5\%$, $P < 0.05$), and the two follow-up assessments did not differ significantly from post-training scores (Fig. 2).

For trials 2–5, results demonstrated a significant main effect of assessment for mean AI [$F(2.14, 74.88) = 30.92, P < 0.001$, partial $\eta^2 = 0.47$]. Pairwise comparisons indicated that pre-training AI was lower than for all other assessments (mean AI difference $\pm$ SE: $11.1 \pm 1.4\%$, $P < 0.008$). Also, AI scores at both follow-up assessments were higher compared to post-training (Fig. 2) (mean AI difference $\pm$ SE: $5.6 \pm 1.3\%$, $P < 0.05$). There was no observed effect of training group or an interaction between group and assessment.

Measures of contralateral M1 cortical excitability

Data were found to significantly violate the assumptions of normality for SP MEP, SICI and ICF. Following successful log transformation, no significant differences in SP MEP, SICI or ICF were observed between groups or across assessments. Data were normally distributed for CSP across all subjects. No significant group or assessment differences in CSP duration were observed, nor was an interaction between main effects seen. Data were normally distributed for each threshold (rMT, aMT and 1mVT). For rMT, there was a main effect of assessment [$F(2.32, 81.27) = 4.96, P = 0.007$, partial $\eta^2 = 0.12$]. Pairwise comparisons revealed that rMT was higher following training ($P < 0.008$) compared with other assessments (Fig. 3). Multivariate tests did demonstrate a significant interaction effect for this term [Wilks' $\lambda = 0.78, F(3,33) = 3.085, P = 0.04$, partial $\eta^2 = 0.22$]. The day training group demonstrated higher aMT values across all assessments [$F(1,35) = 4.85, P = 0.034$, partial $\eta^2 = 0.12$ and higher 1 mVT values [Wilks' $\lambda = 0.78, F(3,33) = 2.98, P = 0.046$, partial $\eta^2 = 0.21$].

Actigraphic assessment of sleep quality

Measures of sleep quality did not substantially violate the assumptions of normality and homogeneity of variance. No significant differences between training groups and nights of sleep were found, nor was an interaction effect between group and night observed ($P > 0.05$).

Relationship between tracking performance and cortical excitability

AI was not significantly related to SP or PP measures of CE at pre- or post-training. At 12-h follow-up, SICI and ICF were correlated with AI, $r = -0.50, -0.54$, and predictive of AI, $R^2 = 0.48, \beta_s = -0.08, -0.15$ (Fig. 4). When examining the day training group at 12-h follow-up, SICI remained correlated with AI, $r = -0.42$, but ICF was no longer significantly related to AI. The regression model was also not significant for SICI and ICF. In the night training group, SICI was not significantly associated with AI, $r = -0.34$, but ICF was correlated with AI, $r = -0.65$. The regression model exhibited significant predictive value of SICI and ICF for AI, $R^2 = 0.45, \beta_s = -0.03, -0.17$ for the night group. At 24-h assessment, PP measures were not predictive of variance of tracking accuracy in either group.

Tracking performance was not correlated with CSP at any assessment for either group.

At pre-training assessment, AI was positively correlated with rMT, $r = 0.25$, $P < 0.05$, but not with aMT or 1 mVT. As the sole predictor, rMT was not a significant predictor of the variance in AI, $R^2 = 0.06$, $\beta = 0.25$, $P = 0.08$. When 1 mVT was added in the model, the model reached significance, $R^2 = 0.16$, $\beta_s = -0.65$, -0.50 , $P = 0.02$. A significant relationship was not observed between thresholds and AI immediately following training or at follow-up assessments.

Discussion

The primary results of this work support previous literature indicating that motor skills can continue to develop following training but sleep following training did not confer additional benefits to this observed offline skill development. A second major finding was that measures of cortical excitability were modified by skill training and predictive of tracking skill performance 12 h after training.

Sleep and skill learning

Finger-tracking skill performance improved following training, and improvement was not only retained after 12- and 24-h intervals but was also enhanced compared to post-training level of skill. This enhancement was not significantly greater after an interval containing sleep versus an interval containing only waking activity following training. These findings suggest that time of day did not significantly affect initial skill acquisition or immediate performance. The improvement in skill performance demonstrates that rapid skill acquisition occurred for this goal-directed, visuospatial finger-tracking skill. These data extend previous results for a similar training paradigm (Borich et al. 2011) by investigating the role of sleep in the offline consolidation of tracking skill after training.

Sleep has been shown to benefit learning for a number of motor skills (Stickgold et al. 2000a; Walker et al. 2002; Huber et al. 2004) yet here, results did not indicate a substantive benefit of sleep following training compared to an equivalent period of waking activity. It was hypothesized that the skill employed here may preferentially benefit from sleep following training due to the complexity of the task. The task required continuous visuomotor processing to accurately track a moving target and was designed as a more complex motor skill than skills used in previous experimental designs (Stickgold et al. 2000b; Walker et al. 2002; Robertson et al. 2005). However, this may not have been the case. Although the tracking apparatus is novel, controlled movements of the dominant index finger with on-line movement correction occur repeatedly during daily skills. This does make the selected motor task an attractive tool to assess 'real life' motor ability and functional hand control in patient populations (Carey et al. 2002; Bhatt et al. 2007), but it may lack the required complexity to challenge a healthy neuromuscular system. Supporting this speculation were the rapid improvements in tracking performance observed within the first skill assessment. As discussed previously, sleep has been shown to benefit tasks that are more complex (Kuriyama et al. 2004; Robertson et al. 2004; Cohen et al. 2005) while the mere passage of time provides greater benefit to less complex motor skills (Cohen et al. 2005; Cohen and Robertson 2007).

Previous work demonstrating a beneficial effect of sleep in post-training skill development has primarily utilized serial reaction finger-tapping sequence learning (Walker et al. 2003a; Kuriyama et al. 2004; Robertson et al. 2005), where skill is acquired without conscious awareness. Skill can also be explicitly acquired with this task paradigm (Robertson et al. 2004; Doyon et al. 2009). Reaction time and number of repeated sequences completed correctly are usual indicators of performance. In both sequence learning paradigms, robust enhancement of skill performance in terms of reaction time, but not accuracy, is observed after a night of sleep. Results also suggest that explicit awareness of the task and increased complexity of the task benefit from sleep to a greater extent than simple, implicit sequence learning (Kuriyama et al. 2004; Robertson et al. 2004; Cohen et al. 2005).

Sequential tapping motor skill learning may have limited “real life” application to (re)learning of functional skills although serial reaction time learning impairments have been observed in clinical populations (Ferraro et al. 1993; Willingham et al. 1997). The main transferrable component of this skill is the discrete nature of the task since many functional activities are multistep processes. Yet, these multistep processes are primarily learned with explicit awareness of the goal of the task and the outcome of the movement produced. Also, the multistep nature of functional tasks typically occurs over a different time span compared to repeated sequencing of finger movements as quickly as possible. Finger-sequence learning also differs from most functional skills in terms of the perceptual demands required for successful performance. Finger tapping uses a visual cue presented sequentially to prompt a key press but rarely is feedback provided to allow for online performance adjustment. Therefore, minimal feed-forward or feedback processing is required to complete the task successfully. As a result, it is likely that this skill uses different motor control strategies based on the time constraints and information used to produce skilled movement compared functional motor skills (Schmidt 2005).

Relatedly, reaction time as a measure of skill proficiency has limited application to functional task performance. Skills are rarely performed with speed of movement as the goal. Far more often, the quality or accuracy of the movement is what is meaningful. The differences between discrete finger-tapping sequence learning and continuous visuospatial finger-tracking learning are substantial enough to explain the apparent discrepancy in the beneficial role for sleep in offline memory enhancement for these two types of motor skill. Other motor learning paradigms are in agreement with the findings from this investigation, suggesting sleep-dependent motor skill memory enhancement is contingent on the nature of the skill to be learned.

The influence of sleep on motor skill learning has also been examined using two other types of motor skills that are continuous in nature: dynamic visuomotor adaptation and implicit visuospatial tracking. In both paradigms, movement is continuous, and a continuous kinematic measure of accuracy is collected, usually pathway deviation. It has been shown that in either case, offline motor skill stabilization and even enhancement occur following training that is not dependent on sleep during this stage in young, healthy individuals (Shadmehr and Brashers-Krug 1997; Doyon et al. 2009). Another motor skill that shares many common features with the finger-tracking task employed here is implicit visuospatial tracking skill, where the subject is able to see the target and the cursor but visual

feedforward or feedback information is not available. Using this task, Siengsukon and Boyd (2008) demonstrated the absence of offline skill enhancement in young, healthy individuals following sleep. Additionally, no increases in tracking accuracy were observed following waking. These data support previous conclusions that certain implicit skill learning does not benefit significantly from sleep and were extended to a continuous tracking skill. The additional explicit information provided here did not result in sleep-dependent offline consolidation of finger-tracking skill but did benefit from the passage of time following training for continued skill development.

Another factor to consider in sleep and motor skill learning paradigms is the effect of circadian rhythms and time of day of training and/or skill assessment. Recent investigations have begun to separate these effects by training subjects and assessing skill performance at different times of day. Keisler et al. (2007) showed that skill performance improvements overnight were not significantly greater than improvements observed for a group that had the same amount of skill practice but did not sleep between assessments. These data highlight the limitation of assessing skill performance only before and after sleep since the overnight improvements observed may simply be a recovery of skill performance, rather than an actual indicator of skill learning. The authors argue that the results indicate that the systematic variance in time of day creates a significant confound in typical sleep and learning studies. A similar training paradigm corroborated (Cai et al. 2009) these findings and contrasted previous work, indicating a significant role for sleep in the offline consolidation of sequence skill learning (Fischer et al. 2002; Walker et al. 2002, 2003a).

Our work has attempted to control for this potential confounding effect by assessing performance of all subjects after an interval with and without sleep after training has occurred. Our findings suggest that sleep did not simply reverse the negative time of day effect of skill performance assessment in the evening immediately following training since subjects trained during the day also demonstrated similar performance improvement over a day of waking activity. Additionally, improvements at 12-h follow-up, regardless of time of assessment, were maintained at 24-h follow-up. Therefore, this study design demonstrated offline skill consolidation that could not be explained by factors solely associated with time of day such as fatigue, motivation or attention (Matthews et al. 2000).

In an effort to control for practice effects that may have been associated with repeated trials of the same waveform, within-assessment analyses were conducted to evaluate trial-by-trial tracking performance. During pre-training skill assessment, there was a significant improvement from the first trial to the next four trials. Importantly, this within-assessment trial effect was only observed at pre-training. This suggests that between-session skill consolidation was not due to practice-dependent improvement within a given assessment but, rather, retention of previously acquired information over time. This does not preclude the potential that subtle within-assessment skill improvements occurred during retention testing, but it does indicate that skill acquired during the initial visit was retained for at least 24 h following training regardless of experimental group. The lack of within-assessment differences between trials immediately following training supports that asymptotic performance occurred and the lack of a trial effect at either 12-h follow-up session argues against significant improvements in tracking skill performance due to repeated exposure to

the test waveform. These results indicate that the majority of skill acquisition took place during the pre-training assessment and between-session skill retention occurred for the acquired information that was not influenced by type of post-training interval.

Taken together, our results combined with previous work argue that the beneficial effect of sleep on post-training information processing is task-dependent. It appears that continuous, explicit, visuospatial finger-tracking skill development is not sensitive to post-training level of activity or arousal. These findings, combined with previous studies, suggest that sleep-dependent consolidation likely occurs for tasks that are discrete in nature, do not rely on substantial perceptual processing and have performance evaluated by reaction time rather than accuracy over time.

Skill learning and cortical excitability

The relationship between skill learning and neural activity was also probed. An expected increase in cortical excitability was not observed following training in either training group. In fact, rMT was significantly higher across groups after training, indicating reduced cortical excitability, specifically at the neuronal membrane level (Wassermann 2008). These data indicate that one episode of skilled finger-tracking training does not significantly increase immediate post-training excitability in the contralateral M1. Previous work using various neuroimaging approaches has demonstrated involvement of M1 in skill acquisition and post-training memory consolidation. Other work has demonstrated increases in M1 excitability immediately following training (Muellbacher et al. 2001; Gallasch et al. 2009). Here, significant acquisition was not accompanied by expected increases in M1 excitability. This may have been due to a number of factors. It appears that skill proficiency was rapidly attained; therefore, expected increases in M1 excitability may have transiently occurred over the 20-min training session and/or during pre-training skill assessment. Previous work has shown that once a motor skill has been learned, increases in M1 excitability are no longer observed (Floyer-Lea and Matthews 2004; Gallasch et al. 2009). The authors suggest this may be due to changes in activity patterns associated with changes in skill performance (Floyer-Lea and Matthews 2004). Other research has demonstrated dynamic shifts in cortical activation can occur rapidly or gradually depending on the type of motor skill trained and the relative degree to which learning has occurred over time (Koenke et al. 2006). This shift may occur across different time periods depending on the skill learned and the training paradigm employed (Floyer-Lea and Matthews 2004; Koenke et al. 2006).

We previously reported decreased corticospinal excitability directly following training using the same tracking apparatus and similar training paradigm (Borich et al. 2011). Here, increased rMT values, suggesting decreased excitability at the neuronal membrane level, were observed following training. We speculate that once significant skill acquisition occurred for visuospatial finger tracking, a shift in cortical activity from M1 to either subcortical or parietal associative cortices or both could explain the observed reduction in M1 excitability. This was not investigated in this study but could be empirically tested by serially assessing rMT throughout the training period to determine whether dynamic shifts in excitability during skill acquisition. Previous work has demonstrated that early skill performance is associated with widespread cortical activation but once a skill is successfully

learned, efficient and localized neural processing is associated with successful performance (Walker et al. 2005; Orban et al. 2010). Therefore, dynamic changes in brain activity patterns from those associated with naive performance to those related to proficient may explain the observed reductions in cortical excitability after training. It may also explain the relationship between skill performance and intracortical M1 excitability at follow-up assessments, where increased intracortical inhibition in M1 was associated with increased skill performance.

Regression analyses demonstrated a significant relationship between intracortical M1 excitability and tracking performance at 12-h follow-up assessment. Higher SICI and lower ICF, indicating increased intracortical inhibition, values were associated with better tracking performance. These results compliment recent findings demonstrating a relationship between levels of SICI and level of tracking skill at 24-h follow-up assessment (Borich et al. 2011). Here, we demonstrate a relationship between motor skill proficiency and intracortical excitability regardless of post-training interval. Combined these results suggest that decreases in intracortical excitability are associated with increases in finger-tracking accuracy between pre-training and skill retention assessments. Interestingly, this relationship was no longer observed at twenty-four follow-up assessment. There may be multiple explanations for these findings. Contralateral M1 may be differentially recruited based on the amount and time of exposure to 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). It appears that this 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). As discussed above, our results and previous research suggest 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 shift may occur across different time periods depending on the skill learned and the training paradigm (Floyer-Lea and Matthews 2004; Koenke et al. 2006). Here, the lack of relationship between intracortical excitability at the second follow-up assessment was also accompanied by a lack of significant continued skill development between the first and second follow-up assessments. This finding may also support the idea that once a skill is learned, there is no longer an association between contralateral M1 activity and skill performance. This was not the primary aim of this investigation but may be an important consideration in future motor learning paradigms with serial follow-up assessments.

Investigations using rTMS to produce a virtual lesion to a specific cortical region have allowed for inference of causal relationships between localized brain regions and behavior that are time-dependent. Contralateral M1 has been shown to be necessary for post-training memory consolidation for ballistic (Muellbacher et al. 2002) and implicit sequence (Robertson et al. 2005) motor skill learning, but not for dynamic adaptation (Baraduc et al. 2004) or explicit, continuous, visuospatial skill learning (Borich et al. 2011). Using the same tracking apparatus, Carey et al. (2006) demonstrated that rTMS-induced disruption of contralateral M1 did not affect initial skill acquisition but, when applied to the ipsilateral cortex, early skill acquisition was decreased. These interventional studies demonstrate that the importance of M1, both contralateral and ipsilateral to the trained extremity, for motor

skill learning is dependent on both the type of skill learned and stage of information processing.

The results here demonstrate a substantial learning effect with modest changes in cortical excitability in the contralateral M1. It may be that other cortical regions were involved to a greater extent in this type of skill learning. Or, as argued above, excitability changes in M1 may have been transient and insignificant once the training period was completed. Also, the relationship between specific sleep stages and skill learning was not the focus of this inquiry but, as discussed previously, prior work has demonstrated relationships between sleep stage oscillatory activity using EEG and offline skill learning (Walker et al. 2002; Huber et al. 2004). Future work should utilize multimodal neuroimaging approaches to simultaneously monitor multiple brain regions over the time course of skill development to understand the interconnected relationships between motor regions of the brain at different stages of memory processing. Multimodal imaging during sleep may also provide important information regarding brain behavior during different states of arousal with different oscillatory properties (Bergmann et al. 2009; Massimini et al. 2009). Findings from these future studies will aid in the interpretation of results from work utilizing a single neuroimaging technique or research focused on a specific cortical region.

The conclusions drawn from this work, combined with related studies in patient populations, provide a foundation to evaluate the relationship between sleep, changes in neural activity and the time course of continuous visuospatial motor skill learning in individuals following neurologic insult. A greater understanding of these processes and relationships from this investigation in healthy individuals now provides normative data to compare to future results in neurologic patient populations. Continuing this line of inquiry will ultimately provide a comprehensive evaluation of the therapeutic potential of sleep that will inform future rehabilitation paradigms in an effort to maximize skill (re)learning and restoration of function following neurologic injury.

Acknowledgments

This publication was made possible by support from the National Center for Research Resources' (NCRR) grant M01 RR00400, a component of the National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIH or NCRR. This study was also supported by a Doctoral Dissertation Fellowship from the University of Minnesota Graduate School (M.B.).

References

- Baraduc P, Lang N, Rothwell JC, Wolpert DM (2004) Consolidation of dynamic motor learning is not disrupted by rTMS of primary motor cortex. *Curr Biol* 14:252–256 [PubMed: 14761660]
- Bergmann TO, Groppa S, Seeger M, Molle M, Marshall L, Siebner HR, Bergmann TO, Groppa S, Seeger M, Molle M, Marshall L, Siebner HR (2009) Acute changes in motor cortical excitability during slow oscillatory and constant anodal transcranial direct current stimulation. *J Neurophysiol* 102:2303–2311 [PubMed: 19692511]
- Bhatt E, Nagpal A, Greer KH, Grunewald TK, Steele JL, Wiemiller JW, Lewis SM, Carey JR, Bhatt E, Nagpal A, Greer KH, Grunewald TK, Steele JL, Wiemiller JW, Lewis SM, Carey JR (2007) Effect of finger tracking combined with electrical stimulation on brain reorganization and hand function in subjects with stroke. *Exp Brain Res* 182:435–447 [PubMed: 17562035]

- Borich M, Furlong M, Holsman D, Kimberley TJ (2011) Goal-directed visuomotor skill learning: off-line enhancement and the importance of the primary motor cortex. *Restor Neurol Neurosci* 29:105–113 [PubMed: 21701062]
- Buyse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiat Res* 28:193–213
- Cai DJ, Rickard TC, Cai DJ, Rickard TC (2009) Reconsidering the role of sleep for motor memory. *Behav Neurosci* 123:1153–1157 [PubMed: 20001099]
- Carey J, Bogard C, King B, Suman V (1994) Finger-movement tracking scores in healthy subjects. *Percept Mot Skills* 79:563–576 [PubMed: 7808897]
- Carey J, Bogard C, Youdas J, Suman V (1995) Stimulus-response compatibility effects in a manual tracking task. *Percept Mot Skills* 81:1155–1170 [PubMed: 8684911]
- Carey JR, Kimberley TJ, Lewis SM, Auerbach E, Dorsey L, Rundquist P, Ugurbil K (2002) Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain* 125:773–788 [PubMed: 11912111]
- Carey JR, Fregni F, Pascual-Leone A (2006) rTMS combined with motor learning training in healthy subjects. *Restor Neurol Neurosci* 24:191–199 [PubMed: 16873974]
- Chen R, Tam A, Butefisch C, Corwell B, Ziemann U, Rothwell JC, Cohen LG (1998) Intracortical inhibition and facilitation in different representations of the human motor cortex. *J Neurophysiol* 80:2870–2881 [PubMed: 9862891]
- Classen J, Liepert J, Wise SP, Hallett M, Cohen LG (1998) Rapid plasticity of human cortical movement representation induced by practice. *J Neurophysiol* 79:1117–1123 [PubMed: 9463469]
- Cohen DA, Robertson EM (2007) Motor sequence consolidation: constrained by critical time windows or competing components. *Exp Brain Res* 177:440–446 [PubMed: 17021894]
- Cohen DA, Pascual-Leone A, Press DZ, Robertson EM (2005) Offline learning of motor skill memory: a double dissociation of goal and movement. *Proc Nat Acad Sci USA* 102:18237–18241 [PubMed: 16330773]
- Doyon J, Korman M, Morin A, Dostie V, Hadj Tahar A, Benali H, Karni A, Ungerleider LG, Carrier J (2009) Contribution of night and day sleep vs. simple passage of time to the consolidation of motor sequence and visuomotor adaptation learning. *Exp Brain Res* 195:15–26 [PubMed: 19277618]
- Ferraro FR, Balota DA, Connor LT, Ferraro FR, Balota DA, Connor LT (1993) Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with senile dementia of the Alzheimer type: a serial reaction time (SRT) investigation. *Brain Cogn* 21:163–180 [PubMed: 8442933]
- Field A (2009) *Discovering statistics using SPSS: (and sex, drugs and rock'n' roll)*. Sage, London
- Fischer S, Hallschmid M, Elsner AL, Born J (2002) Sleep forms memory for finger skills. *Proc Nat Acad Sci USA* 99: 11987–11991 [PubMed: 12193650]
- Floyer-Lea A, Matthews PM (2004) Changing brain networks for visuomotor control with increased movement automaticity. *J Neurophysiol* 92:2405–2412 [PubMed: 15381748]
- Gallasch E, Christova M, Krenn M, Kossev A, Rafolt D, Gallasch E, Christova M, Krenn M, Kossev A, Rafolt D (2009) Changes in motor cortex excitability following training of a novel goal-directed motor task. *Eur J Appl Physiol* 105:47–54 [PubMed: 18807065]
- Goedert KM, Willingham DB, Goedert KM, Willingham DB (2002) Patterns of interference in sequence learning and prism adaptation inconsistent with the consolidation hypothesis. *Learn Mem* 9:279–292 [PubMed: 12359837]
- Hikosaka O, Miyasita K, Miyachi S, Sakai K, Lu X (1998) Differential roles of the frontal cortex, basal ganglia and cerebellum in visuomotor sequence learning. *Neurobiol Learn Mem* 70:137–149 [PubMed: 9753593]
- Hikosaka O, Nakamura K, Sakai K, Nakahara H (2002) Central mechanisms of motor skill learning. *Curr Opin Neurobiol* 12:217–222 [PubMed: 12015240]
- Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC (1973) Quantification of sleepiness: a new approach. *Psychophysiology* 10:431–436 [PubMed: 4719486]
- Hotermans C, Peigneux P, de Noordhout AM, Moonen G, Maquet P, Hotermans C, Peigneux P, de Noordhout AM, Moonen G, Maquet P (2008) Repetitive transcranial magnetic stimulation over the

- primary motor cortex disrupts early boost but not delayed gains in performance in motor sequence learning. *Eur J Neurosci* 28:1216–1221 [PubMed: 18783369]
- Howell DC (2007) Statistical methods for psychology. Thomson Wadsworth, Belmont, California
- Huber R, Ghilardi MF, Massimini M, Tononi G (2004) Local sleep and learning [see comment]. *Nature* 430:78–81 [PubMed: 15184907]
- Inghilleri M, Berardelli A, Marchetti P, Manfredi M (1996) Effects of diazepam, baclofen and thiopental on the silent period evoked by transcranial magnetic stimulation in humans. *Exp Brain Res* 109:467–472 [PubMed: 8817277]
- Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 14:540–545 [PubMed: 1798888]
- Karni A, Meyer G, Jezard P, Adams MM, Turner R, Ungerleider LG (1995) Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 377:155–158 [PubMed: 7675082]
- Keisler A, Ashe J, Willingham DT, Keisler A, Ashe J, Willingham DT (2007) Time of day accounts for overnight improvement in sequence learning. *Learn Mem* 14:669–672 [PubMed: 17911369]
- Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey LL, Lojovich JM, Carey JR (2004) Electrical stimulation driving functional improvements and cortical changes in subjects with stroke. *Exp Brain Res* 154:450–460 [PubMed: 14618287]
- Kimberley TJ, Borich MR, Prochaska KD, Mundfrom SL, Perkins AE, Poepping JM, Kimberley TJ, Borich MR, Prochaska KD, Mundfrom SL, Perkins AE, Poepping JM (2009) Establishing the definition and inter-rater reliability of cortical silent period calculation in subjects with focal hand dystonia and healthy controls. *Neurosci Lett* 464:84–87 [PubMed: 19686807]
- Koenke S, Lutz K, Herwig U, Ziemann U, Jancke L (2006) Extensive training of elementary finger tapping movements changes the pattern of motor cortex excitability. *Exp Brain Res* 174:199–209 [PubMed: 16604315]
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. *J Physiol* 471:501–519 [PubMed: 8120818]
- Kuriyama K, Stickgold R, Walker MP (2004) Sleep-dependent learning and motor-skill complexity. *Learn Mem* 11:705–713 [PubMed: 15576888]
- Maeda F, Gangitano M, Thall M, Pascual-Leone A, Maeda F, Gangitano M, Thall M, Pascual-Leone A (2002) Inter- and intra-individual variability of paired-pulse curves with transcranial magnetic stimulation (TMS). *Clin Neurophysiol* 113:376–382 [PubMed: 11897538]
- Massimini M, Tononi G, Huber R (2009) Slow waves, synaptic plasticity and information processing: insights from transcranial magnetic stimulation and high-density EEG experiments. *Eur J Neurosci* 29:1761–1770 [PubMed: 19473231]
- Matthews GRD, Westerman SJ, Stammers RB (2000) Human performance: cognition, stress and individual differences. Taylor and Francis, Philadelphia
- Morgenthaler T, Alessi C, Friedman L, Owens J, Kapur V, Boehlecke B, Brown T, Chesson A, Jr, Coleman J, Lee-Chiong T, Pancer J, Swick TJ, Standards of Practice C, American Academy of Sleep M (2007) Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep* 30:519–529 [PubMed: 17520797]
- Muellbacher W, Ziemann U, Boroojerdi B, Cohen L, Hallett M (2001) Role of the human motor cortex in rapid motor learning. *Exp Brain Res* 136:431–438 [PubMed: 11291723]
- Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, Boroojerdi B, Poewe W, Hallett M (2002) Early consolidation in human primary motor cortex. *Nature* 415:640–644 [PubMed: 11807497]
- Oldfield R (1971) The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9(1):97–113 [PubMed: 5146491]
- Orban P, Peigneux P, Lungu O, Albouy G, Breton E, Laberrenne F, Benali H, Maquet P, Doyon J, Orban P, Peigneux P, Lungu O, Albouy G, Breton E, Laberrenne F, Benali H, Maquet P, Doyon J (2010) The multifaceted nature of the relationship between performance and brain activity in motor sequence learning. *Neuroimage* 49:694–702 [PubMed: 19732838]

- Portney L, Watkins M (2000) Foundations of clinical research: applications to practice. Appleton & Lange, Norwalk, CN
- Robertson EM, Pascual-Leone A, Press DZ (2004) Awareness modifies the skill-learning benefits of sleep. *Curr Biol* 14:208–212 [PubMed: 14761652]
- Robertson EM, Press DZ, Pascual-Leone A (2005) Off-line learning and the primary motor cortex [see comment]. *J Neurosci* 25: 6372–6378 [PubMed: 16000627]
- Rosler KM, Petrow E, Mathis J, Ara'nyi Z, Hess CW, Magistris MR (2002) Effect of discharge desynchronization on the size of motor evoked potentials: an analysis. *Clin Neurophysiol* 113: 1680–1687 [PubMed: 12417220]
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 120:2008–2039 [PubMed: 19833552]
- Rossini PM, Berardelli A, Deuschl G, Hallett M, Maertens de Noordhout AM, Paulus W, Pauri F (1999) Applications of magnetic cortical stimulation. The international federation of clinical neurophysiology. *Electroencephalogr Clin Neurophysiol-Suppl* 52:171–185 [PubMed: 10590986]
- Sadeh A, Sharkey KM, Carskadon MA (1994) Activity-based sleep-wake identification: an empirical test of methodological issues. *Sleep* 17:201–207 [PubMed: 7939118]
- Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I, Sakai K, Ugawa Y, Terao Y, Hanajima R, Furubayashi T, Kanazawa I (1997) Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. *Exp Brain Res* 113:24–32 [PubMed: 9028772]
- Sanger TD, Garg RR, Chen R (2001) Interactions between two different inhibitory systems in the human motor cortex. *J Physiol* 530:307–317 [PubMed: 11208978]
- Schmidt RA (2005) Motor control and learning: a behavioral emphasis. Human Kinetics, Champaign
- Shadmehr R, Brashers-Krug T (1997) Functional stages in the formation of human long-term motor memory. *J Neurosci* 17:409–419 [PubMed: 8987766]
- Siengsukon CF, Boyd LA (2008) Sleep enhances implicit motor skill learning in individuals poststroke. *Top Stroke Rehabil* 15:1–12 [PubMed: 18250068]
- Stickgold R, James L, Hobson JA (2000a) Visual discrimination learning requires sleep after training [see comment]. *Nature Neurosci* 3:1237–1238 [PubMed: 11100141]
- Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA (2000b) Visual discrimination task improvement: a multi-step process occurring during sleep. *J Cogn Neurosci* 12:246–254 [PubMed: 10771409]
- Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, Fishbein W, Tucker MA, Hirota Y, Wamsley EJ, Lau H, Chaklader A, Fishbein W (2006) A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiol Learn Mem* 86:241–247 [PubMed: 16647282]
- Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning [see comment]. *Neuron* 35:205–211 [PubMed: 12123620]
- Walker MP, Brakefield T, Hobson JA, Stickgold R (2003a) Dissociable stages of human memory consolidation and reconsolidation [see comment]. *Nature* 425:616–620 [PubMed: 14534587]
- Walker MP, Brakefield T, Seidman J, Morgan A, Hobson JA, Stickgold R (2003b) Sleep and the time course of motor skill learning. *Learn Mem* 10:275–284 [PubMed: 12888546]
- Walker MP, Stickgold R, Alsop D, Gaab N, Schlaug G (2005) Sleep-dependent motor memory plasticity in the human brain. *Neuroscience* 133:911–917 [PubMed: 15964485]
- Wassermann EM (2008) The Oxford handbook of transcranial stimulation. Oxford University Press, Oxford
- Willingham DB, Peterson EW, Manning C, Brashear HR, Willingham DB, Peterson EW, Manning C, Brashear HR (1997) Patients with Alzheimer's disease who cannot perform some motor skills show normal learning of other motor skills. *Neuropsychology* 11: 261–271 [PubMed: 9110332]
- Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996a) The effect of lorazepam on the motor cortical excitability in man. *Exp Brain Res* 109:127–135 [PubMed: 8740215]

- Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996b) Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. *Ann Neurol* 40:367–378 [PubMed: 8797526]
- Ziemann U, Rothwell JC, Ridding MC (1996c) Interaction between intracortical inhibition and facilitation in human motor cortex. *J Physiol* 496:873–881 [PubMed: 8930851]
- Ziemann U, Muellbacher W, Hallett M, Cohen LG (2001) Modulation of practice-dependent plasticity in human motor cortex. *Brain* 124:1171–1181 [PubMed: 11353733]
- Ziemann U, Ilic TV, Pauli C, Meintzschel F, Ruge D, Ziemann U, Ilic TV, Pauli C, Meintzschel F, Ruge D (2004) Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex [erratum appears in *J Neurosci* 2004 Nov 17;24(46):1 p following 10552 Note: Iliac, Tihomir V [corrected to Ilic, Tihomir V]]. *J Neurosci* 24:1666–1672 [PubMed: 14973238]

c

Measure of cortical excitability	Proposed cortical activity probed
resting motor threshold (rMT)	cortical neuron membrane, Na ⁺ -gated ion channels ¹
active motor threshold (aMT)	cortical neuron membrane, Na ⁺ -gated ion channels ¹
1mV threshold (1mVT)	cortical neuron membrane, Na ⁺ -gated ion channels ¹
single-pulse motor evoked potential (SP MEP)	general corticospinal activity ²
short-interval intracortical inhibition (SICI)	primarily intracortical GABA _A -mediated synaptic activity ³
intracortical facilitation (ICF)	primarily intracortical glutamate-mediated synaptic activity ¹
cortical silent period (CSP)	intracortical GABA _B -mediated synaptic activity ⁴
Measure of sleep quality	Description
time asleep (min)	time between sleep onset and final awake time
sleep latency (min)	time between time into bed and sleep onset
awakenings (#)	number of separate epochs awake
time awake (min)	total time awake during the sleep interval
average time awake (min)	time awake/awakenings
sleep efficiency (%)	time asleep/total time in bed*100

d

Group	Age	Gender	EHI	PSQI	ESS	SSS (pre)	SSS (post)	SSS (12hr)	SSS (24hr)
Day Skill	23.2 ± 3.9	M:10, F:10	74.4 ± 21.5	4.6 ± 2.3	6.7 ± 3.2	2.3 ± 1.1	2.3 ± 1.1	2.2 ± 1.3	2.4 ± 0.9
Night Skill	21.9 ± 3.8	M:10, F:10	77.7 ± 20.9	4.0 ± 1.8	7.9 ± 4.0	2.6 ± 0.9	2.7 ± 1.3	2.4 ± 1.0	2.1 ± 0.8

EHI: Edinburgh Handedness Inventory, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale, SSS: Stanford Sleepiness Scale

Fig. 1.

a Schema of experimental design, **b** Finger-tracking apparatus with splint affixed to the subject's right hand and test waveform displayed on the computer, **c** List of dependent measures of cortical excitability and sleep quality, **d** No differences in subject characteristics were observed between day and night skill training groups ($P > 0.05$). ¹(Ziemann et al. 1996b), ²(Chen et al. 1998), ³(Ziemann et al. 1996a), ⁴(Inghilleri et al. 1996)

Fig. 2.

Changes in skill performance (AI $\pm$ SE) across assessments. Pre-training tracking accuracy was significantly lower than those of all assessments after training when assessing both trial 1 alone and trials 2–5 (* $P < 0.0001$). Tracking skill continued to develop following training, and improvements were maintained for at least one day after training (** $P < 0.012$). No differences in skill performance were observed between day and night training groups

Fig. 3.

Cortical excitability was reduced following training (%MSO $\pm$ SE). Across training groups, rMT values were increased after training, indicating reduced cortical excitability, compared to pre-training and both follow-up assessments (* $P < 0.05$), *MSO* maximum stimulator output

Fig. 4.

The relationship between intracortical excitability and tracking accuracy was significant at 12-h follow-up assessment across training groups. *Left* Greater intracortical inhibition (SICI) was associated with better tracking accuracy (AI). *Right* Lower intracortical facilitation (ICF) was associated with higher AI values. Together, level of intracortical excitability was predictive of tracking accuracy at 12-h follow-up assessment where lower levels of excitability were associated with better skill performance, $R^2 = 0.48$, $P < 0.0001$