Practice with Sleep Makes Perfect: Sleep-Dependent Motor Skill Learning

Matthew P. Walker,[1] Tiffany Brakefield,
Alexandra Morgan, J. Allan Hobson,
and Robert Stickgold
Laboratory of Neurophysiology
Department of Psychiatry
Harvard Medical School
74 Fenwood Road
Boston, Massachusetts 02115

Summary

Improvement in motor skill performance is known to continue for at least 24 hr following training, yet the relative contributions of time spent awake and asleep are unknown. Here we provide evidence that a night of sleep results in a 20% increase in motor speed without loss of accuracy, while an equivalent period of time during wake provides no significant benefit. Furthermore, a significant correlation exists between the improved performance overnight and the amount of stage 2 NREM sleep, particularly late in the night. This finding of sleep-dependent motor skill improvement may have important implications for the efficient learning of all skilled actions in humans.

Introduction

There is growing evidence that sleep represents a critical brain state and time window for the consolidation of certain types of memory (Maquet, 2001; Stickgold et al., 2001). While the specificity of this relationship is still debated (Peigneux et al., 2001), recent reports suggest that sleep may be particularly important for the consolidation of procedural-based skill learning (Maquet, 2001; Peigneux et al., 2001; Stickgold et al., 2001).

In the sensory domain, it has been shown that the ability of humans to perform a perceptual skill task requiring visual discrimination improves across a night of sleep (Karni et al., 1994; Stickgold et al., 2000a). Furthermore, these sleep-induced performance gains in visual learning appear to depend on both the amount of deep non-rapid eye movement (NREM) sleep early in the night and the amount of rapid eye movement (REM) sleep late in the night (Gais et al., 2000; Karni et al., 1994; Stickgold et al., 2000b). With respect to the motor system, Smith and MacNeill (1994) have demonstrated that selective sleep deprivation can impair retention of a pursuit rotor task, inferring that the performance decrement resulted specifically from the loss of stage 2 NREM sleep. Nevertheless, much of the recent data regarding sleep-dependent skill learning in humans has concentrated on the visual system, with less focus on other sensorimotor processes.

A patent feature of procedural motor skill learning is the amount of training that strongly influences subsequent improvement in performance and functional neu-

ral changes (Karni, 1996; Karni and Sagi, 1991, 1993; Sanes and Donoghue, 2000). Although it is an old adage that "practice makes perfect," recent findings suggest that training is not the only determinant of motor skill learning. Time is also an important factor (Karni et al., 1998). Several studies have demonstrated that, while practice produces gains in both speed and accuracy of motor performance within a session, when retested 24 hr later with no further training, significant additional gains in motor performance are apparent (Brashers-Krug et al., 1996; Karni et al., 1998; Shadmehr and Brashers-Krug, 1997).

It seems reasonable to conclude that these additional time-dependent performance gains, which continue in the absence of further training, represent ongoing changes within the brain. However, it remains completely unknown whether this improvement is simply a factor of time or whether it is more strictly dependent on time spent in a specific brain state, that of either wake or sleep, or even a specific stage of sleep. Here we present evidence that continued improvement on a motor skill task occurs only across a night of sleep, while an equivalent period of wake offers no significant benefit to performance and that more than half the variance in overnight improvement can be explained by the amount of stage 2 NREM sleep obtained during the last quarter of the night. These findings may have important practical and theoretical implications for skill learning.

Results

Subjects were trained and subsequently retested on a finger tapping task (see Experimental Procedures). The task was a computerized version of the one previously demonstrated to show delayed learning after 24 hr (Karni et al., 1998). Performance was defined as the number of repeated five-keypress sequences completed in a 30 s trial.

Initial Training Profiles
62 subjects were trained on the motor skill task over 12 30 s trials at either 10 a.m. or 10 p.m. (Figure 1). Subjects trained at 10 a.m. and 10 p.m. showed similar learning, differing by only 2.3% (0.52 sequences) at the end of training. Overall, performance improved by 8.42 sequences (59.3%) across the twelve training trials, with 5.51 sequences (38.8%) occurring across the first three trials (2.75 seq/trial). A slower but relatively constant rate of improvement was seen across the final ten trials, accounting for the remaining 2.91 sequences (20.5%; 0.32 seq/trial).

Group A: Continued Motor Skill Learning across Wake
In order to determine whether the simple passage of time led to consolidation of motor learning, and to investigate potential circadian factors, ten subjects were retested at 4 hr intervals across the day following training at 10 a.m. Compared to post-training performance (the
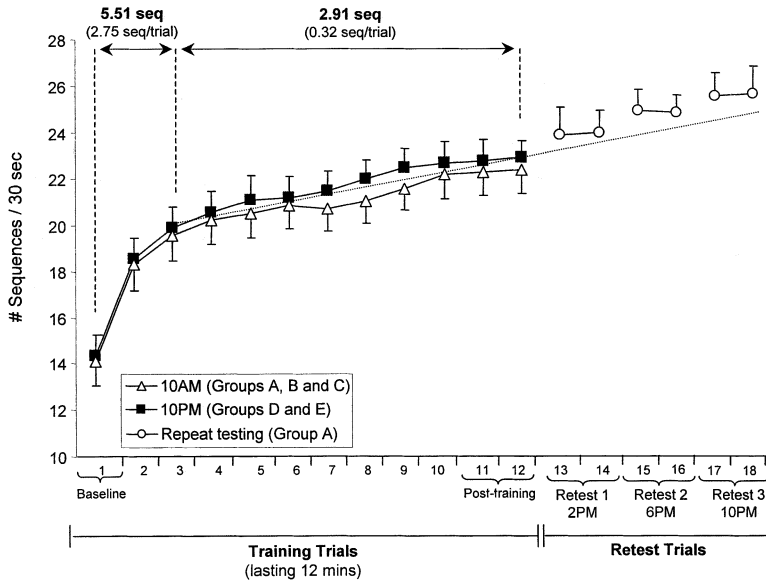
[1]Correspondence: mwalker@hms.harvard.edu

Figure 1. Improvement in Motor Skill Performance (Speed) across Training and Retests

Subjects trained at either 10 a.m. (open triangles, groups A–C) or 10 p.m. (closed squares, groups D and E) showed similar improvement across the 12 trials, differing by only 2.3% at the end of training. Overall performance improved by 59.3% across the 12 training trials, with 38.8% occurring across the first three trials, and the remaining 20.5% occurring at a slower but relatively constant rate across the final ten trials. The projected retest improvement based on the final ten trials is modeled by the dotted line, which assumes improvement based only on continued rehearsal (i.e., trial count) and not time. Repeat testing across the day for subjects in group A, training at 10 a.m. (open circles) produce only a slow incremental improvement similar to that predicted by task repetition alone (dotted line).

average of the last two training trials), there was a slow, linear increase in performance across the three retest points at 2 p.m., 6 p.m. and 10 p.m. [Figure 1, open circles; repeated measures ANOVA, $F_{(3,9)} = 5.2$, $p = 0.006$], averaging 1.08 sequences per retest. Since performance was improving at the rate of 0.32 sequences per trial at the end of training, we could expect an improvement during a two-trial retest of 0.64 sequences based on continued rehearsal alone (Figure 1, dotted line). Although the average improvement at each of the three retest sessions at 2 p.m., 6 p.m., and 10 p.m. was consistently higher than the predicted 0.64 sequences, the incremental increases were not significantly greater than that predicted by rehearsal alone (paired t tests, $p > 0.6$ for each time, $p > 0.25$ for all times combined). The error rate also did not differ significantly across these time points [mean = 2.75 errors/trial, $F_{(3,9)} = 0.19$, $p = 0.90$]. Thus, the simple passage of time during the day produced no significant improvement beyond that expected on the basis of continued rehearsal.

Group B: Continued Motor Skill Learning following Wake and Then Sleep
To determine whether subsequent sleep could offer more significant motor skill improvement compared with wake, 15 subjects were trained at 10 a.m. and then retested once at 10 p.m. after 12 hr of wake, and again at 10 a.m. the next morning following a night of sleep. Similar to those in group A, the subjects demonstrated a nonsignificant 3.9% (0.94 sequences) improvement in performance after 12 hr of wake at 10 p.m. [$t_{(14)} = 1.5$, $p = 0.13$; Figure 2A], similar to that predicted by task repetition alone (0.64 sequences). In contrast, at the second retest the next morning, performance had improved by 18.9% (4.33 sequences) compared with the post-training score 24 hr earlier [$t_{(14)} = 4.6$, $p < 0.0005$] and 14.4% (3.39 sequences) from the night before [$t_{(14)} = 5.4$, $p < 0.0001$]. Furthermore, the actual overnight improvement (as opposed to total score) was significantly greater than prior waking improvement [$t_{(14)} =$

3.2, $p = 0.001$]. The amount of improvement that occurred at 12 hr was not significantly different from that seen in group A at the first retest [+4 hr wake; $t_{(23)} = 0.61$, $p = 0.54$], but was significantly less than seen at the third retest after 12 hr in group A [$t_{(23)} = 2.38$, $p = 0.02$]. This provides further support for the hypothesis that the improvement in group A after 12 hr resulted from task repetition and not the simple passage of time. No significant difference in error rate occurred across the three testing sessions in group B [mean = 3.66 errors/trial; $F_{(2,14)} = 2.58$, $p = 0.09$]. Therefore, 12 hr of wake provided no significant improvement in motor skill learning, yet by 24 hr, following a night of sleep, large significant gains in motor skill performance were apparent.

Group C: Continued Motor Skill Learning following Wake with Hand Rest and Then Sleep
An alternative explanation of these results is that motor activity during the 12 hr wake period following training prevented motor skill consolidation. To eliminate this possibility, ten subjects were trained at 10 a.m. and then wore mittens for 11 hr to prevent skilled finger movements before being retesting at 10 p.m. and again the next morning at 10 a.m. after a night of sleep. At 10 p.m., following 12 hr of wake with hand rest, performance was a nonsignificant 4.3% (0.90 sequences) better compared with the end of training at 10 a.m. that morning [$t_{(9)} = 1.5$, $p = 0.08$; Figure 2B] and similar to that predicted by task repetition. However, the next morning, performance had improved a significant 19.7% (4.30 sequences) compared to the prior evening [$t_{(9)} = 4.6$, $p < 0.002$]. In addition, there was a significant difference in error rate across post-training and retest conditions [$F_{(2,9)} = 8.2$, $p = 0.003$]. Compared to post-training values, the number of errors increased following 12 hr of wake [3.3/trial post-training versus 5.1/trial retest 1; $t_{(9)} = 2.9$, $p < 0.02$], but returned to similar post-training baseline values the next morning [2.7/trial; $t_{(9)} = 1.3$, $p = 0.23$], although now significantly better than at the
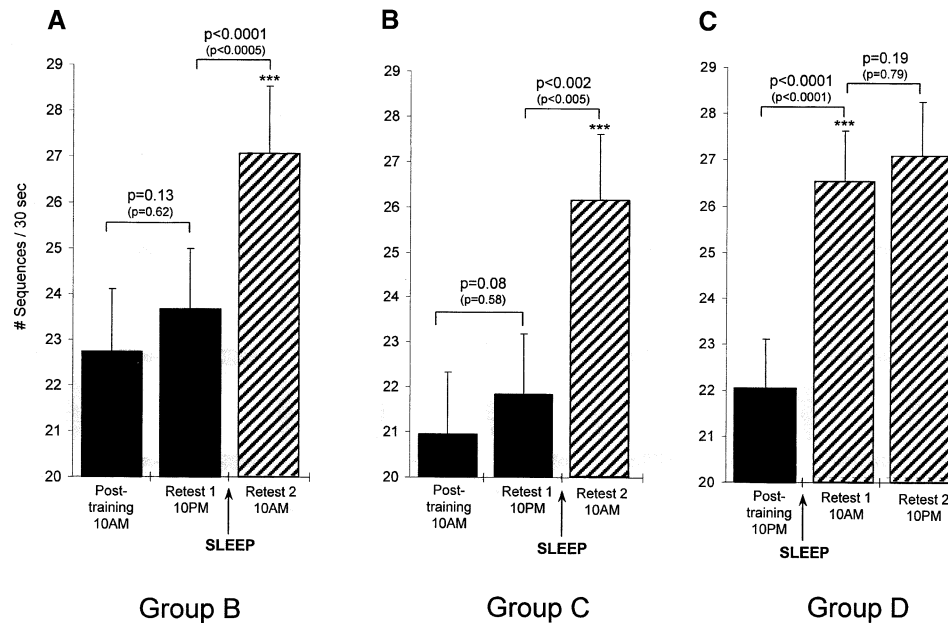
Figure 2. Differential Effects of Sleep and Wake on Continued Motor Skill Learning across 24 Hr

Subjects in groups B and C, trained at 10 a.m. in the morning ([A and B], post training, closed bars) demonstrated no significant improvement in performance following 12 hr of wake (retest 1, closed bars) either without (A) or with (B) hand rest as a control for potential interference. However, following a night of sleep (retest 2, hatched bars [A and B]), performance improved significantly in both groups. In contrast, subjects in group D, trained in the evening ([C], closed bar) immediately showed a significant improvement just 12 hr after training, following a night of sleep (retest 1, hatched bar), but displayed no further significant improvement with an additional 12 hr of wake (retest 2, hatched bar). P values in parentheses represent t tests using an expected difference of 0.64 sequences, based on two trials of task repetition. ***Significant values, p < 0.002.

first retest the night before [t(9) = 3.3, p < 0.01]. Thus, the lack of daytime improvement does not appear to be due to interference from skilled motor activity across the day.

Group D: Continued Motor Skill Learning following Sleep and Then Wake

A second possible explanation of the overnight improvement is that there is simply a delay of more than 12 hr following training before the improvement/consolidation is expressed. To investigate this possibility, 15 subjects were trained at 10 p.m. in the evening and retested the next morning at 10 a.m., after a night of sleep, and again later that day at 10 p.m. Following a night of sleep, a significant 20.5% (4.50 sequences) improvement in motor skill performance (speed) was already apparent after 12 hr at 10 a.m. the next morning compared with post-training scores [t(14) = 10.1, p < 0.0001; Figure 2C], far in excess of that predicted by task repetition alone. However, after an additional 12 hr of wake, only a negligible 2.0% [0.53 sequences] improvement was seen [t(14) = 1.3, p = 0.2]. Therefore, the overnight improvement in group D was significantly greater than in the subsequent 12 hr of waking [t(14) = 5.8, p < 0.0001]. No significant differences in accuracy occurred across these testing sessions [mean = 2.66 errors/trial; F(2,14) = 0.99, p = 0.38].

Based on the findings of groups A–D, we conclude that (1) all subjects improved similarly within the initial 12 training blocks, regardless of their time of training,

(2) motor skill improvement showed a slow incremental increase with repeated testing across the day, similar to that predicted by simple task repetition, and with no apparent circadian influences, (3) 12 hr of wake, either with or without hand rest, offered only a small, nonsignificant benefit to learning, and (4) a night of sleep provided a highly significant improvement in performance with no decrement in accuracy, regardless of whether the sleep period came during the first or the second 12 hr after training.

Since improvement occurred during the night but not during the day, sleep itself appeared to be the most likely cause of this delayed improvement. From the findings of groups A–D alone, however, it remains possible that some unknown nocturnal circadian process and not sleep per se produced this improvement. The correlation between overnight improvement and various sleep stage parameters in the final group of subjects below investigated this question.

Group E: Correlation between Continued Motor Skill Learning and Sleep

Twelve subjects were trained at 10 p.m., spent the night in the sleep laboratory, and were retested at 10 a.m. the next morning. Once again, a significant 17.9% (4.41 sequences) improvement was seen at 10 a.m. following the night of sleep (df = 11, t = 5.2, p < 0.0005), without any loss of accuracy [mean = 2.45 errors/trial; t(11) = 1.4, p = 0.17].

When sleep stage scores were correlated with the
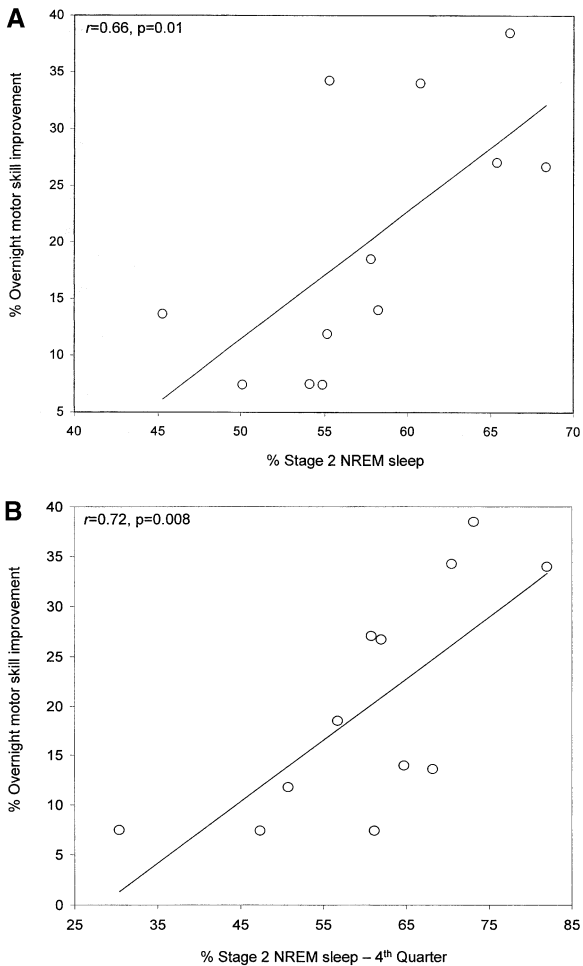
A r=0.66, p=0.01

B r=0.72, p=0.008

Figure 3. Relationship between Overnight Improvement and Stage 2 NREM Sleep Measures

Correlation plot of the percentage of overnight improvement in motor skill performance (speed) and the total percentage of stage 2 NREM sleep (A), and with the percentage of stage 2 NREM sleep in the fourth quarter of the night (B) in group E.

increase in motor skill performance, a significant relationship was evident between the total percentage of stage 2 NREM sleep and the percentage of overnight motor skill improvement [r(10) = 0.66, p = 0.01; Figure 3A]. No other stage of sleep displayed a significant correlation with improvement (Table 1).

Since previous studies have demonstrated the existence of specific sleep windows for learning (Smith and Butler, 1982; Stickgold et al., 2000b), the night of sleep was divided into quarters, and the correlation of motor improvement with stage 2 sleep was examined across the night. After Bonferroni correction for multiple comparisons [α/number of supplementary comparisons (0.05/4) = 0.012], a significant relationship with the percentage of overnight motor skill improvement was seen only for the percentage of stage 2 NREM sleep in the last quarter of the night [r(10) = 0.72 p = 0.008; Figure 3B]. Stage 2 in each of the first three quarters of the night showed no significant correlation (Table 1).

Discussion

Brain State-Dependent Motor Skill Improvement

While practice on the motor skill task improved performance within the training session for all groups equally, subjects went on to demonstrate remarkably different time courses of subsequent motor skill improvement, specifically dependent on sleep. Subjects trained at 10 a.m. in the morning demonstrated no significant improvement when retested after 12 hr of wake, but showed a significant 18.9% improvement at 10 a.m. the following morning. Similarly, subjects trained at 10 p.m. in the evening demonstrated a significant 20.5% improvement overnight, just 12 hr post-training, but showed no significant additional improvement after a further 12 hr of wake. Thus, significant improvement was only seen across a night of sleep and not over a similar period of waking, regardless of whether the time awake or time asleep came first.

The possibility that circadian factors prevented expression of learning after 12 hr of wake is unlikely. First, motor learning across the 12 training trials was similar for subjects trained at 10 a.m. or 10 p.m., as was the case for subjective ratings of alertness across all testing points. Furthermore, repeated testing across the day (group A, Figure 1) showed only a slow linear improvement in performance, similar to that predicted by task repetition, and showed no circadian fluctuations. Likewise, the possibility that the sleep-dependent improvement resulted from hand rest during sleep is unlikely since 11 hr of total hand rest during the day resulted in no significant improvement beyond practice effects and actually led to an increase in errors. Thus, we consider sleep itself to be the most reasonable source of the delayed improvement in motor skill performance.

Sleep Stage-Dependent Motor Skill Improvement

When the degree of overnight motor skill improvement was correlated with sleep stage recordings, a significant positive correlation with the percentage of stage 2 NREM sleep was evident, particularly late in the night. Indeed, as much as 52% of the intersubject variance was explained by this sleep parameter alone.

The relationship between learning and stage 2 NREM is in agreement with the work of Smith and MacNeill (1994). However, the stage 2 relationship is in contrast to several prior studies of visual procedural skill learning, showing predominantly a REM sleep and slow wave sleep (stages 3 and 4 NREM) dependence (Gais et al., 2000; Karni et al., 1994; Stickgold et al., 2000a, 2000b). It is unclear why this difference exists, although we consider several potential explanations. Firstly, there is evidence that the specific sleep stage dependence may be governed by task complexity (Tweed et al., 1999), with more complex skilled tasks showing a greater sensitivity to REM sleep deprivation, while relatively simple tasks appear more sensitive to stage 2 deprivation. Secondly, within the procedural domain, variations in sleep stage dependence may reflect a distinction between the input (sensory/perceptual) and output (motor) roles of these systems, each of which could require functionally different brain states for effective consolidation. Compli-

Table 1. Correlative Relationships between Sleep Stage Percentage Scores and the Percentage of Motor Skill Improvement across the Night

Sleep Stage	Sleep %	Correlation Coefficient (r)	Significance (p)
Stage 1 NREM	3.1 (±0.68)	0.41	0.17
Stage 2 NREM	52.1 (±1.94)	0.66	0.01*
Stage 3 NREM	10.2 (±0.85)	−0.26	0.40
Stage 4 NREM	11.4 (±1.51)	−0.17	0.59
REM	18.4 (±2.05)	−0.32	0.30
Stage 2: 1st Quarter	40.1 (±4.24)	0.29	0.35
Stage 2: 2nd Quarter	52.9 (±2.91)	0.18	0.56
Stage 2: 3rd Quarter	55.7 (±2.77)	0.08	0.79
Stage 2: 4th Quarter	59.6 (±3.88)	0.72	0.008*

Values in parentheses represent standard errors. (A combination of stages 3 and 4 NREM sleep ["slow wave sleep"] also did not result in a significant relationship with overnight improvement r = −0.49; p = 0.10).
NREM, nonrapid eye movement sleep; REM, rapid eye movement sleep.
*Significant correlations.

mentary to these notions are findings indicating the development of unique forms of cortical plasticity in response to different forms of sensory motor tasks (Jenkins et al., 1990; Recanzone et al., 1992a, 1992b).

While only correlative, it is interesting to speculate that stage 2 sleep, the most prolific stage of all human sleep, may offer the required mechanisms for continued motor skill improvement. In particular, sleep spindles, a defining electrophysiological characteristic of stage 2, may facilitate sleep-related information consolidation (Sejnowski and Destexhe, 2000). Spindles are brief but powerful bursts of synchronous neuronal firing (7–14 Hz) in thalamo-cortical networks that reach peak density late in the night (De Gennaro et al., 2000). Spindles are thought to cause massive calcium entry into pyramidal cells of the cerebral cortex, triggering intracellular, cal-
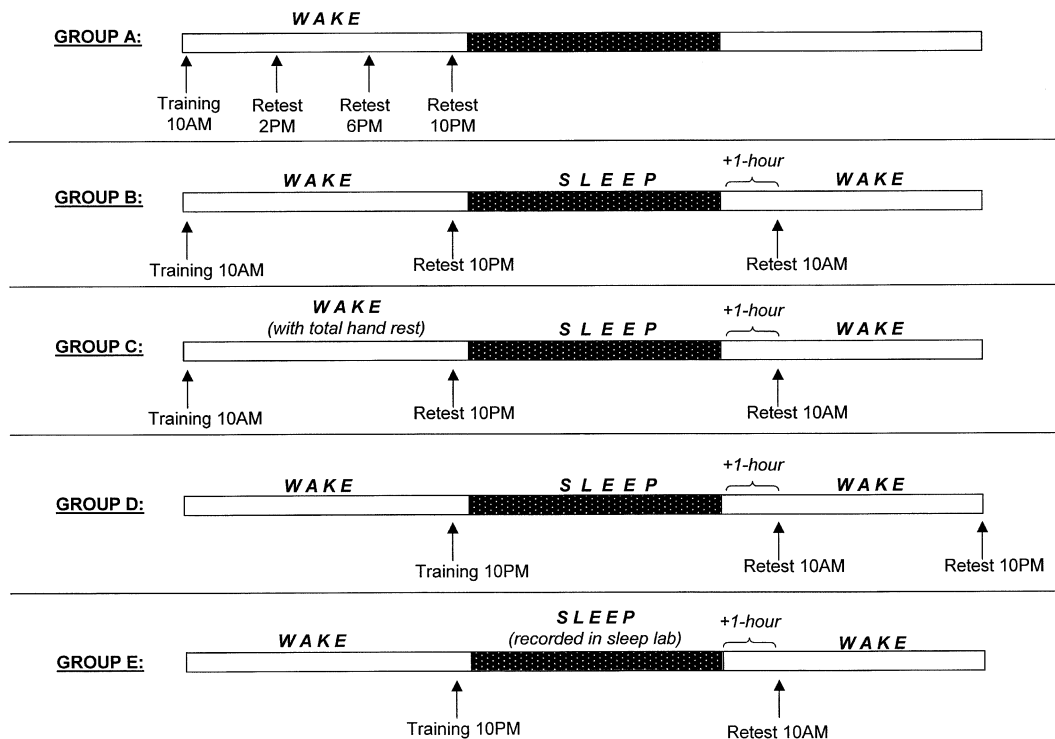

Figure 4. Experimental Protocol

62 subjects were allocated into five experimental groups (A–E) and either trained at 10 a.m. or 10 p.m. on day 1. They were then retested across the following 12–24 hr period with different retest schedules.
Group A: Trained at 10 a.m. and retested at 2 p.m., 6 p.m., and 10 p.m.
Group B: Trained at 10 a.m. and retested after 12 hr of wake and again after an additional 12 hr following a night of sleep.
Group C: Identical to group B, except that subjects wore mittens on both hands from 10:15 a.m. until 9 p.m. as a control for potential motor interference from dexterous finger movements.
Group D: Trained at 10 p.m. and retested 12 hr later immediately following a night of sleep and again following an additional 12 hr of wake.
Group E: Trained at 10 p.m., and following a full night of recorded sleep, retested at 10 a.m. the next morning.

cium-dependent mechanisms required for synaptic plasticity (Sejnowski and Destexhe, 2000) and have been shown to increase following training on a motor task (Fogel et al., 2001). However, we do not suggest that the neurophysiological medium required for this type of learning is exclusive to sleep. Similar mechanisms may occur during periods of quiet wake at a less efficacious quality and/or quantity, although such an effect was not apparent in the investigations reported here.

Implications for Motor Skill Learning in Humans

These findings have important implications for procedural learning in general and for motor skill learning in particular. Delayed improvement in performance across 24 hr has been reported previously in a number of motor skill studies (Brashers-Krug et al., 1996; Karni et al., 1998; Liu and Wrisberg, 1997), which we now expect will show a similar nocturnal sleep dependency. The potential implications become most significant, however, in the broader context of acquiring real-life skillful actions—for example, learning motor patterns required for movement-based sports, learning a musical instrument, or developing artistic movement control. All such learning of new actions may require sleep before the maximum benefit of practice is expressed. This may be especially important in early human development, where sleep percentages also peak (Salzarulo and Fagioli, 1995), or in functional recovery following insults to the motor system (Hallett, 2001). These findings now add to a growing set of data suggesting that many, if not all, sensorimotor skills may require post-training sleep for the optimal consolidation of learning and furthermore that this dependence may be sleep-stage specific.

Experimental Procedures

Participants

The study cohort consisted of 62 right-handed subjects between the ages of 18 and 25 (mean age 22.4 ± 2.3 [SD]; 41 females and 21 males). Subjects had no prior history of drug or alcohol abuse, neurological, psychiatric, or sleep disorders and were instructed to be drug-, alcohol-, and caffeine-free for 12 hr prior to and during the study period. All studies were approved by the local human studies committee, and all subjects provided written informed consent.

Motor Skill Task

The sequential finger tapping task required subjects to press four numeric keys on a standard computer keyboard with the fingers of their left (nondominant) hand, repeating the five element sequence, 4-1-3-2-4, "as quickly and as accurately as possible" for a period of 30 s. The numeric sequence (4-1-3-2-4) was displayed at the top of the screen at all times to exclude any working memory component to the task. Each key press produced a white dot on the screen, forming a row from left to right, rather than the number itself, so as not to provide accuracy feedback. The computer recorded the key press responses, and each 30 s trial was automatically scored for the number of complete sequences achieved (speed) and the number of errors made (accuracy). Training consisted of twelve 30 s trials with 30 s rest periods between trials and lasted a total of 12 min. The score (speed and accuracy) from the first trial of the training session was taken as the "baseline" measure, while the averaged scores from the final two trials were taken as the "post-training" performance.

Experimental Design

The 62 subjects were divided into five experimental groups and were trained within a half hour of either 10 a.m. or 10 p.m. on

day 1. Each group subsequently underwent a specific schedule of retests (±30 min). At each retest, subjects performed two 30 s trials of the same sequence spaced by a 30 s rest period, with the scores again being averaged. All morning retests were performed at least 1 hr after awakening. The retest schedules (Figure 4) were as follows:

Group A (continued motor skill learning across wake; n = 10): Subjects were trained at 10 a.m. and retested at 2 p.m., 6 p.m., and 10 p.m.

Group B (continued motor skill learning following wake and then sleep; n = 15): Subjects were trained at 10 a.m. and retested 12 and 24 hr later.

Group C (continued motor skill learning following wake with hand rest and then sleep; n = 10): Subjects were trained at 10 a.m. and retested 12 and 24 hr later as in group B, but wore mittens on both hands from 10:15 a.m. until 9 p.m. During this time, subjects were continuously monitored and only allowed to watch movies and read. Subjects could only remove the mittens for bathroom breaks. At 9 p.m., the mittens were removed (although dexterous finger movements were still not allowed) to reduce the risk of hand stiffness, and subjects were retested at 10 p.m. Following a night of sleep, subjects were retested again at 10 a.m. the next morning.

Group D (continued motor skill learning following sleep and then wake; n = 15): Subjects were trained at 10 p.m. in the evening and retested 12 and 24 hr later.

Group E (correlation between continued motor skill learning and sleep, monitored in the sleep laboratory; n = 12): Subjects were brought into the sleep laboratory, trained at 10 p.m., and prepared for polysomnographic sleep monitoring using standardized techniques (Rechtschaffen and Kales, 1968). Digital sleep recordings were made with a Grass Colleague system with electrode placements at C3, C4, O1, O2, A1, and A2, left and right outer canthi, and submentally. Following a full night of recorded sleep, they were retested at 10 a.m. the next morning. The sleep records were then scored according to standardized scoring criteria (Rechtschaffen and Kales, 1968). All sleep stage scoring was performed blind to the subject's motor skill performance.

Sleep Quality and Alertness

At each testing point, all subjects completed the Stanford Sleepiness Scale, a standard measure of subjective alertness (Hoddes et al., 1973). There were no significant differences in the Stanford Sleepiness Scale ratings of alertness within any of the groups across test points (p ≥ 0.55 for each). On the seven-point scale (1 being most alert), mean values were as follows: 10 a.m., 2.51; 2 p.m.; 2.20; 6 p.m., 2.40; 10 p.m., 2.32.

Subjects in group E averaged 7.88 ± 0.6 hr (SD) of sleep, defined by sleep laboratory recordings, and displayed normative sleep profiles (Williams, 1978) (Table 1). The amount of overnight sleep obtained by subjects in groups B, C, and D was documented with sleep logs and averaged 7.6 hr of sleep (SD ± 0.56) on the experimental night.

Statistical Analysis

Comparative analyses of experimental variables were carried out using repeated measures, ANOVAs, as well as paired and unpaired Students t tests (two-tailed). Correlations between changes in motor performance and sleep stage variables were performed using Pearson's correlation analyses. Correlations within sleep stage across the four quartiles of the night were corrected using the Bonferonni adjustment of α level (Miller, 1991).

References

Brashers-Krug, T., Shadmehr, R., and Bizzi, E. (1996). Consolidation in human motor memory. Nature *382*, 252–255.

De Gennaro, L., Ferrara, M., and Bertini, M. (2000). Topographical distribution of spindles: variations between and within NREM sleep cycles. Sleep Res. Online *3*, 155–160.

Fogel, S., Jacob, J., and Smith, C. (2001). Increased sleep spindle activity following simple motor procedural learning in humans. Paper presented at: Congress Physiological Basis for Sleep Medicine (Uruguay: Actas de Fisiología).

Gais, S., Plihal, W., Wagner, U., and Born, J. (2000). Early sleep triggers memory for early visual discrimination skills. Nat. Neurosci. *3*, 1335–1339.

Hallett, M. (2001). Plasticity of the human motor cortex and recovery from stroke. Brain Res. Brain Res. Rev. *36*, 169–174.

Hoddes, E., Zarcone, V., Smythe, H., Philips, R., and Dement, W.C. (1973). Quantification of sleepiness: a new approach. Psychophysiology *10*, 431–436.

Jenkins, W.M., Merzenich, M.M., Ochs, M.T., Allard, T., and Guic-Robles, E. (1990). Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. J. Neurophysiol. *63*, 82–104.

Karni, A. (1996). The acquisition of perceptual and motor skills: a memory system in the adult human cortex. Brain Res. Cogn. Brain Res. *5*, 39–48.

Karni, A., and Sagi, D. (1991). Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. Proc. Natl. Acad. Sci. USA *88*, 4966–4970.

Karni, A., and Sagi, D. (1993). The time course of learning a visual skill. Nature *365*, 250–252.

Karni, A., Tanne, D., Rubenstein, B.S., Askenasy, J.J., and Sagi, D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. Science *265*, 679–682.

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M.M., Turner, R., and Ungerleider, L.G. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. Proc. Natl. Acad. Sci. USA *95*, 861–868.

Liu, J., and Wrisberg, C.A. (1997). The effect of knowledge of results delay and the subjective estimation of movement form on the acquisition and retention of a motor skill. Res. Q. Exerc. Sport *68*, 145–151.

Maquet, P. (2001). The role of sleep in learning and memory. Science *294*, 1048–1052.

Miller, R.G., Jr. (1991). Simultaneous Statistical Inference (New York: Springer-Verlag).

Peigneux, P., Laureys, S., Delbeuck, X., and Maquet, P. (2001). Sleeping brain, learning brain. The role of sleep for memory systems. Neuroreport *12*, A111–A124.

Recanzone, G.H., Merzenich, M.M., Jenkins, W.M., Grajski, K.A., and Dinse, H.R. (1992a). Topographic reorganization of the hand representation in cortical area 3b owl monkeys trained in a frequency-discrimination task. J. Neurophysiol. *67*, 1031–1056.

Recanzone, G.H., Merzenich, M.M., and Dinse, H.R. (1992b). Expansion of the cortical representation of a specific skin field in primary somatosensory cortex by intracortical microstimulation. Cereb. Cortex *2*, 181–196.

Rechtschaffen, A., and Kales, A. (1968). A manual standardized terminology, techniques and scoring system for sleep stages of human subjects (Bethesda, MD: US Department of Health).

Salzarulo, P., and Fagioli, I. (1995). Sleep for development or development for waking?–some speculations from a human perspective. Behav. Brain Res. *69*, 23–27.

Sanes, J.N., and Donoghue, J.P. (2000). Plasticity and primary motor cortex. Annu. Rev. Neurosci. *23*, 393–415.

Sejnowski, T.J., and Destexhe, A. (2000). Why do we sleep? Brain Res. *886*, 208–223.

Shadmehr, R., and Brashers-Krug, T. (1997). Functional stages in the formation of human long-term motor memory. J. Neurosci. *17*, 409–419.

Smith, C., and Butler, S. (1982). Paradoxical sleep at selective times following training is necessary for learning. Physiol. Behav. *29*, 469–473.

Smith, C., and MacNeill, C. (1994). Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. J. Sleep Res. *3*, 206–213.

Stickgold, R., James, L., and Hobson, J.A. (2000a). Visual discrimination learning requires sleep after training. Nat. Neurosci. *3*, 1237–1238.

Stickgold, R., Whidbee, D., Schirmer, B., Patel, V., and Hobson, J.A. (2000b). Visual discrimination task improvement: a multi-step process occurring during sleep. J. Cogn. Neurosci. *12*, 246–254.

Stickgold, R., Hobson, J.A., Fosse, R., and Fosse, M. (2001). Sleep, learning, and dreams: off-line memory reprocessing. Science *294*, 1052–1057.

Tweed, S., Aubrey, J.B., Nader, R., and Smith, C.T. (1999). Deprivation of REM sleep or stage 2 sleep differentially affects cognitive procedural and motor procedural memory. Sleep *22*, Suppl. 1, H392.I.

Williams, R.L. (1978). Sleep Disorders: Diagnosis and Treatment (New York: Wiley).