

## ORIGINAL ARTICLE

# Deprivation and Recovery of Sleep in Succession Enhances Reflexive Motor Behavior

Andreas Sprenger<sup>1</sup>, Frederik D. Weber<sup>2</sup>, Bjoern Machner<sup>1</sup>, Silke Talamo<sup>1</sup>, Sabine Scheffelmeier<sup>1</sup>, Judith Bethke<sup>1</sup>, Christoph Helmchen<sup>1</sup>, Steffen Gais<sup>2</sup>, Hubert Kimmig<sup>1,3,4</sup>, and Jan Born<sup>2</sup>

<sup>1</sup>Department of Neurology, University Luebeck, D-23538 Luebeck, Germany, <sup>2</sup>Institute of Medical Psychology and Behavioral Neurobiology and Center for Integrative Neuroscience, University of Tuebingen, D-72076 Tuebingen, Germany, <sup>3</sup>Schwarzwald-Baar Klinikum, D-78052 Villingen-Schwenningen, Germany and <sup>4</sup>Department of Neurology, University Freiburg, D-79106 Freiburg, Germany

Address correspondence to Jan Born, Institute of Medical Psychology, University of Tübingen, Otfried-Müller-Str. 25, 72076 Tuebingen, Germany.  
Email: jan.born@uni-tuebingen.de

## Abstract

Sleep deprivation impairs inhibitory control over reflexive behavior, and this impairment is commonly assumed to dissipate after recovery sleep. Contrary to this belief, here we show that fast reflexive behaviors, when practiced during sleep deprivation, is consolidated across recovery sleep and, thereby, becomes preserved. As a model for the study of sleep effects on prefrontal cortex-mediated inhibitory control in humans, we examined reflexive saccadic eye movements (express saccades), as well as speeded 2-choice finger motor responses. Different groups of subjects were trained on a standard prosaccade gap paradigm before periods of nocturnal sleep and sleep deprivation. Saccade performance was retested in the next morning and again 24 h later. The rate of express saccades was not affected by sleep after training, but slightly increased after sleep deprivation. Surprisingly, this increase augmented even further after recovery sleep and was still present 4 weeks later. Additional experiments revealed that the short testing after sleep deprivation was sufficient to increase express saccades across recovery sleep. An increase in speeded responses across recovery sleep was likewise found for finger motor responses. Our findings indicate that recovery sleep can consolidate motor disinhibition for behaviors practiced during prior sleep deprivation, thereby persistently enhancing response automatization.

**Key words:** behavioral inhibition, express saccades, motor skill learning, sleep, sleep deprivation

## Introduction

Sleep is known to play an important role in the consolidation of newly acquired memory (Rasch and Born 2013). Consequently, the deprivation of sleep hampers memory consolidation. Yet beyond this, deprivation of sleep impairs a number of other cognitive functions. In particular, executive behavioral control via inhibitory mechanisms seems to be largely weakened in

sleep-deprived conditions, thus favoring impulsive responding (Chuah et al. 2006; Drummond et al. 2006; Goel et al. 2009). It is commonly assumed that such impulsivity disappears as soon as sleep is recovered. However, although less efficient (Yoo et al. 2007) the tired brain is still able to learn. Considering that sleep consolidates newly acquired knowledge and skills, it might be expected that recovery sleep ensuing sleep deprivation

also enhances impulsive and reflexive behavior practiced during the period of sleep deprivation.

Express saccades represent a simple model for the study of inhibitory control of reflexive behavior. They refer to distinct, very fast, reflexive responses in the range of 70–130 ms that occur at a certain rate during performance on visuo-motor tasks (Fischer and Boch 1983; Fischer and Ramsperger 1984). Whereas the onset of regular saccades is marked by 2 distinct bursts of activity in superior colliculus neurons, express saccades follow a single burst of activity in superior colliculus (Dorris et al. 1997) along with enhanced activity in lateral intraparietal cortical neurons (Chen et al. 2013), indicating that express saccades constitute a separate entity at the neuronal level. Express saccades are usually suppressed by prefrontal control: projections from the lateral prefrontal cortex to the superior colliculus seem to play an important role, as revealed by single cell recordings in monkey (Tinsley and Everling 2002) as well as human lesion studies (Braun et al. 1992; Müri et al. 1999). The deprivation of sleep as a state of diminished prefrontal executive control is not only associated with faster response times and increased impulsivity to negative stimuli (Anderson and Platten 2011), but has also been linked to increased occurrence of express saccades (Bocca and Denise 2006). Express saccades cannot be performed at will initially; they occur naturally. They can be learned, however, although this is a rather gradual process requiring days of training (Fischer et al. 1984; Fischer and Ramsperger 1986; Fischer and Weber 1993).

Here we investigated how express saccades profit from sleep and sleep deprivation in healthy humans. We employed a standard prosaccade gap paradigm which, aside from regular saccades, typically invokes a certain rate of express saccades (Fischer and Ramsperger 1984). Regular saccades elicited by this paradigm have been shown to be faster after posttraining sleep in a previous study (Gais et al. 2008). In the main experiment of the present study (also comprising subjects of this previous study), we found that the rate of express saccades in the prosaccade gap paradigm is not increased by posttraining sleep per se. Surprisingly, however, sleep produced a long-lasting (4 weeks) increase in express saccades after subjects had briefly performed the prosaccade task in sleep-deprived conditions, suggesting that sleep deprivation primes the learning of express saccades which become consolidated during ensuing recovery sleep. In addition, we show that a similar priming by sleep deprivation can be achieved for finger motor responses.

## Materials and Methods

### Subjects

Ninety-five healthy humans participated in the experiments (35 men, 60 women; mean age  $\pm$  standard deviation:  $22.4 \pm 3.9$  years). Subjects were right-handed and did not take any medication at the time of the experiments. A medical history questionnaire and a routine physical examination were used to exclude volunteers with acute or chronic illness. They had a regular sleep-wake rhythm for at least 6 weeks before the experiments. The subjects participating in laboratory sleep conditions were familiarized with the experimental setting by spending an adaptation night in the laboratory that included the attachment of electrodes for sleep recordings. Subjects were informed about general risks originating from tiredness and inattentiveness after sleep deprivation. Informed written consent was obtained from all participants prior to participation. The study was approved by the local Ethics Committee of the University Lübeck and was conducted in accordance with the Declaration of Helsinki.

## Main Experiments—Express Saccades

### Design and Procedures

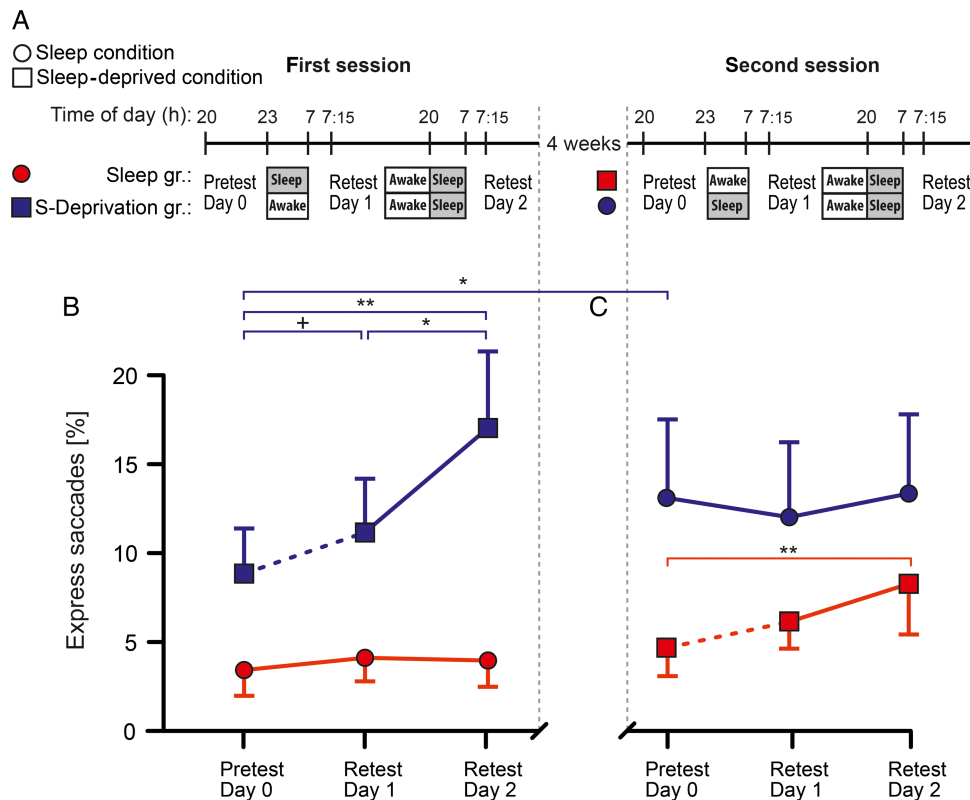
Thirty subjects (14 men, 16 women, age  $22.2 \pm 2.6$  years) were randomly assigned to a sleep and a sleep deprivation (S-Deprivation) group ( $n = 15$  for each group). The sample included 19 subjects from a previous study (Gais et al. 2008) and for the present study was extended by 5 subjects for the Sleep group and 6 subjects for the S-Deprivation group. Procedures and methods were identical across all subjects. On the evening before Day 1, participants of both groups were first subjected to a pretest on a standard prosaccade gap paradigm between 20:00 and 20:30 h, and then to 2 h of prosaccade training on the same task between 20:30 and 22:30 h. Subjects of the Sleep group then slept in the laboratory from 23:00 to 7:00 h the next morning. Because arousals from SWS and REM sleep can influence subsequent recall due to persisting sleep inertia (Stones 1973), subjects were typically awakened from Stage 1 or Stage 2 sleep, although this procedure may not entirely prevent such influence. Subjects were retested on the prosaccade gap paradigm at 7:15 h (Day 1) and  $\sim 24$  h later in the morning of the following day (Day 2). The S-Deprivation group followed the same schedule, except that they stayed awake the night after training and were only allowed to sleep after 18:00 h the following evening (recovery sleep). During sleep deprivation nights, subjects talked to the experimenter and listened to music. Activities straining the eyes (e.g., reading, watching TV) were not permitted. Subjects additionally were asked to press a button every 10 min to ensure wakefulness. After the retest on Day 1, subjects of both groups left the lab to follow their regular daily activities while avoiding any mentally or physically stressful activity (adherence to which was confirmed by a final questionnaire). Additionally, actimetry (Actiwatch AW2, Cambridge Neurotechnology Ltd., Cambridge, UK) was used to confirm that subjects did not nap during daytime. On the second night (before the retest on Day 2), subjects from both groups slept at home.

Subjects of both groups were tested in a second experimental session which took place 4 weeks later. This second session followed the same procedure as the first session, except that according to a cross-over design the subjects of the original Sleep group underwent a night of sleep deprivation, whereas the subjects of the original S-Deprivation group were tested in conditions of regular sleep. Six subjects (3 in each group) dropped out and did not participate in this second session. Figure 1A summarizes the design of the main experiment.

Three additional control groups were run to disentangle contributions of the pretest, the training, and the retest on Day 1 on saccade performance in the S-Deprivation condition (Fig. 2, bottom panel). The procedures for these groups were basically the same as for the first session of the S-Deprivation condition, except that the “No-Pretest/No-train” group ( $n = 15$ , 5 men, 10 women,  $21.2 \pm 3.1$  years) was neither pretested nor trained on the evening before nocturnal sleep deprivation, but only underwent the tests in the morning of Days 1 and 2. The “No-Train” group ( $n = 15$ , 7 men, 8 women,  $25.3 \pm 7.5$  years) was pretested before the nocturnal vigil but did not receive any training, and the “No-Retest” group ( $n = 15$ , 9 men, 6 women,  $21.7 \pm 2.4$  years) was pretested and trained on the task before sleep deprivation, but the retest on Day 1 was omitted.

### Saccade Paradigm

A classic prosaccade gap paradigm with a fixation time (of a centrally located dot) of  $1000 \pm 200$  ms and a gap of 200 ms was used.



**Figure 1.** (A) Procedures for the Sleep and S-Deprivation groups for the original first session (left) and for the second session taking place 4 weeks later (right). Red lines—Sleep group, that is, subjects who had regular sleep on the original first session and were deprived of sleep on the second session; blue lines—S-Deprivation group, that is, subjects who were deprived of sleep on the original first session and had regular sleep on the second session. Shapes of data points indicate actual condition, that is, circles—regular sleep; squares—sleep deprivation. Times of pretest (on Day 0) and retests (on Day 1 and Day 2) are indicated. (B) Mean  $\pm$  SEM express saccade rates at the pretest (on Day 0) and at retests (on Day 1 and Day 2) for the first and (C) second session. Sleep-deprived subjects were allowed to sleep already at 18:00 h but usually went to bed later than that, that is, around 20:00 h, as indicated. Dashed line indicates an intervening night of sleep deprivation. \* $P < 0.1$ , \*\* $P < 0.05$ , \*\*\* $P < 0.01$  for paired tests between conditions.

After the gap, the target stimulus appeared for  $1250 \pm 250$  ms at the new position. Subjects were instructed to fixate the central fixation dot and to look at the upcoming target as quickly and accurately as possible. In test trials, the target was set back to the central position right afterwards. In training trials at the end of the target presentation, the subject's eyes were led back to the central position by smooth pursuit. The target amplitudes were  $5^\circ$ ,  $10^\circ$ ,  $15^\circ$ , and  $20^\circ$  to the left and the right. During task performance, the subject sat in a quiet room in complete darkness, with his/her head placed on a chin rest. Subjects sat 1.4 m in front of a large translucent screen, onto which a red laser dot (used as fixation dot and target, diameter  $0.1^\circ$ ) was projected from the rear.

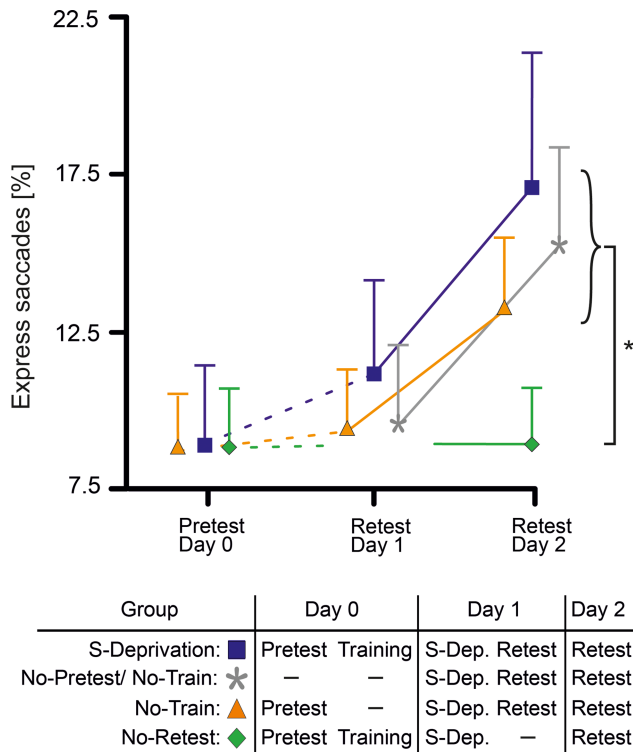
Pretest and retests contained 240 prosaccade trials, with the sequence of target amplitudes and directions occurring in a randomized order. A test contained 50 saccades each with target amplitudes of  $10^\circ$  and  $20^\circ$  to the left and to the right, respectively, and 10 saccades each with target amplitudes of  $5^\circ$  and  $15^\circ$  to the left and right, respectively. The training contained 10 blocks of 100 trials in the same target direction with amplitudes randomized across trials. Target direction during training was counterbalanced across the subject's 2 experimental sessions. In each block,  $40 \times 10^\circ$ ,  $40 \times 20^\circ$ ,  $10 \times 5^\circ$ , and  $10 \times 15^\circ$  saccades were presented.

### Recordings and Analysis of Saccades

Saccade performance during pretest and retests was recorded using a video-based EyeLink II-system (SR Research Ltd.,

Osgoode, ON, Canada) with a 500-Hz sampling rate. These data were filtered with a 100 Hz Gaussian filter ( $-3$ db). During training, eye movements were registered by electro-oculography (EOG): Ag/AgCl electrodes were positioned supraorbital and infraorbital of the left eye (for vertical movements) and at the outer corners of both eyes (for horizontal movements). A ground electrode was fixed on the forehead. EOG data were amplified by a DC amplifier (Tönnies, Högberg, Germany; low-pass filter 300 Hz; amplification factor  $50 \mu\text{V/U}$ ).

Saccade data from test and training epochs were analyzed semi-automatically. Saccadic eye movements were identified based on an initial eye velocity of  $>30^\circ/\text{s}$  and a peak velocity reached within the succeeding 60 ms. The beginning and end of a saccade were defined by the points at which velocity crossed  $20^\circ/\text{s}$ . All detected saccades were screened manually, and artifacts were excluded. Saccadic latency (i.e., the saccadic reaction time), peak velocity, and accuracy (i.e., the gain defined by the saccade amplitude divided by the target amplitude) were determined. Express saccades were defined by reaction times between 70 and 130 ms and thus separated from "regular saccades" with latencies between 130 and 400 ms, which is a standard procedure accounting for the bimodal distribution of reaction times typically obtained with the gap paradigm (Fischer and Ramsperger 1986). Only saccades that were in the correct direction and accurate, that is, with gains between 0.5 and 1.5 (Gais et al. 2008), were included in the analyses. We also analyzed so-called predictive saccades, that is, anticipatory saccades with reaction times



**Figure 2.** Mean  $\pm$  SEM express saccade rates at the pretest (on Day 0) and retests (on Day 1 and Day 2) of the original S-Deprivation group (squares filled blue), and 3 additional groups which, like the S-Deprivation group, were subjected to sleep deprivation between Day 0 and Day 1. Of these groups (see bottom panel), different from the original S-Deprivation group, the No-Pretest/No-train group (grey asterisks) did neither perform the Pretest nor saccade training on Day 0, the No-train group (triangles filled yellow) did not perform the training on Day 0, and the No-Retest group (diamonds filled green) did not perform the retest on Day 1. Dashed lines indicate intervening night of sleep deprivation. (At pretest on Day 0 express rates were quite similar for the respective groups, i.e.,  $8.94 \pm 2.49\%$  for the original S-Deprivation group,  $8.69 \pm 1.83\%$  for the No-Train group, and  $8.80 \pm 1.86\%$  for the No-Retest group; respective group differences are hardly distinguishable.) \* $P < 0.05$ , for the difference between performance of the No-Retest group and performance of each of the other 3 groups at the retest on Day 2.

$<70$  ms that occur at random in either the right or wrong direction, to separate effects of express saccades from those of other types of saccades (see [Supplementary Table 1](#) including legend).

## Sleep

Recordings of sleep during adaptation and experimental nights were based on standard polysomnography, including electroencephalographic (EEG) recordings from C3 and C4 (referenced to electrodes attached to the mastoids) as well as vertical and horizontal EOG and EMG recordings (from electrodes over the left and right musculus mentalis). Signals were amplified (Brain Amp, Brain Products, Germany) and digitized, with the signals sampled at a rate of 500 Hz and a resolution of 0.1 and 0.5  $\mu$ V for EEG and EOG, respectively. The EEG was filtered between 0.16 and 250 Hz; EOG signals were DC-recorded. Sleep stages were determined offline for subsequent 30-s recording epochs following standard criteria ([Rechtschaffen and Kales 1968](#)). Total sleep time (TST) and the time spent in the different sleep stages [wake; Stages 1, 2, 3, and 4; and rapid eye movement (REM) sleep] were calculated in minutes and percentage of TST. SWS was defined as the sum of time spent in Stages 3 and 4 sleep. Latencies of SWS and REM sleep were assessed with reference to sleep onset.

## Supplementary Experiments—Finger Press Responses

### Subjects, Procedure, and Design

To compare sleep deprivation-related effects on express saccades with those in other motor systems, in a supplementary study 20 additional subjects (age  $22.0 \pm 2.0$  years, all female) were tested on a simple 2-choice finger motor task. The subjects were randomly allocated to a Sleep ( $n = 10$ ) and an S-Deprivation group ( $n = 10$ ). Subjects of both groups first performed the finger motor task in the morning of Day 1 after a night of regular sleep or a night of sleep deprivation depending on their group without any pretesting or training before this night (corresponding to the No-Pretest/No-Train condition of the main experiments). Design and procedures were otherwise identical to those of the main experiment (Fig. 3A). Each subject was tested only at 1 session.

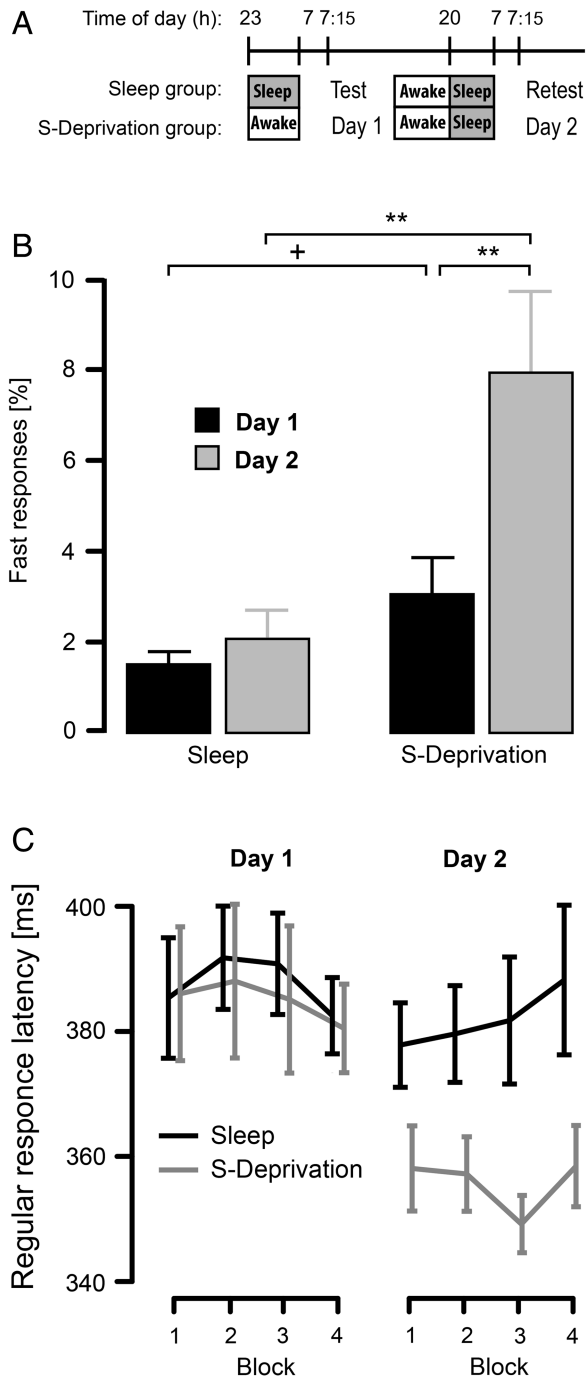
### Two-Choice Finger Motor Task

The task required the subject to fixate a white circle of  $1^\circ$  diameter on a black background in the center of the screen which disappeared after  $1250 \pm 250$  ms. Following a blank period of 200 ms (gap), the circle reappeared with the right or the left half filled, and the subject was asked to press the corresponding left or right button with the ipsilateral index finger as fast and as accurately as possible. Four hundred milliseconds after the button press, the screen turned blank (black) for  $1650 \pm 150$  ms. During task performance, the participant sat in a quiet room in complete darkness, 0.6 m in front of a computer monitor. The head was placed on a chin rest; index fingers were each placed on a response button. To ensure correct fixation and absence of saccades during testing, eye movements were recorded as described for the main experiments.

Reaction time on Days 1 and 2 was assessed in 4 blocks of 60 trials each with left and right response trials occurring in pseudo-random order. Erroneous button presses were rare ( $0.92 \pm 0.19\%$ ) and were discarded from analyses. Corresponding to the differentiation of regular and express saccades, we defined finger motor responses with latencies  $>275$  ms as “regular” finger presses, and responses with latencies between 150 and 275 ms as very fast “express-like finger responses.” This criterion excludes physiologically impossible responses  $<130$  ms that would have to be classified as premature and matches the  $<1.25$  standard deviations from the mean cut-off typically accounting also for express saccades. None of the responses included in the analysis were faster than 172 ms.

### Statistical Analyses

For the first experimental session, statistical significance was assessed using analyses of variance with the between-subject factor “Group” (e.g., Sleep vs. S-Deprivation), and the repeated-measures factor “Test” (pretest, retest on Day 1, retest on Day 2). Data of the second session in the main experiment were analyzed separately, because there were obvious effects of sleep deprivation that persisted and affected already pretest performance in the second session. Also, due to dropouts, sample size was reduced in this second session. Because data failed to show normality (Shapiro–Wilk tests for normality), we conducted exploratory Friedman tests on the 3 testing points of the second session, separately for the 2 groups. Subsequent analysis of variance and nonparametric post hoc tests (Wilcoxon’s signed rank test) were focused on the pretest and testing on Day 2, that is,



**Figure 3.** (A) Procedures for the Sleep and S-Deprivation groups of the supplementary study on finger motor responses. Times of the first test (on Day 1) and the retest (on Day 2) are indicated. (B) Mean  $\pm$  SEM percentage of very fast responses (latencies 150–275 ms) at the test on Day 1 and at the retest on Day 2 between the groups. \* $P < 0.1$ , \*\* $P < 0.01$ , for t-test between groups and test conditions, respectively. (C) Reaction times (in ms) for regular responses (latencies  $\geq 275$  ms) for each of the 4 blocks during the test and the retest for the Sleep (black lines) and S-Deprivation groups (gray lines). Sleep-deprived subjects were allowed to sleep already at 18:00 h but usually went to bed later, that is, around 20:00 h, as indicated.

the time points with the clearest effect in the first session and the direct test of a sleep effect. Degrees of freedom were corrected using the Greenhouse–Geisser procedure where appropriate. Pairwise comparisons were done using Student's t-tests unless

otherwise reported. A  $P$ -value of  $< 0.05$  was considered significant. Ages are reported as mean  $\pm$  standard deviation, other data as mean  $\pm$  standard error of the mean.

## Results

In the main experiments, 2 groups of subjects, a Sleep and an S-Deprivation group, were tested according to procedures illustrated in Figure 1A. For each test and retest, the subject's proportion of express saccades was determined.

### Sleep Deprivation Followed by Recovery Sleep Promotes Persistent Increase in Express Saccades

The proportion of express saccades was strongly affected depending on whether subjects slept or stayed awake on the night after training ( $F_{1.4, 38.8} = 6.7$ ,  $P = 0.008$ , for Group  $\times$  Test interaction, Fig. 1B). In the Sleep group, the rate of express saccades remained unchanged across the 3 test occasions, that is, across pretest and the retests on Days 1 and 2 ( $F_{2,28} = 0.6$ ,  $P = 0.55$ ). In contrast, the subjects of the S-Deprivation group displayed a slight increase in the proportion of express saccades on Day 1 right after the wake night in comparison with the pretest level which, however, did not reach significance ( $t_{(14)} = -1.9$ ,  $P = 0.074$ ). Interestingly, this increase was followed by a further significant increase in express saccades across the ensuing night of recovery sleep ( $t_{(14)} = -2.6$ ,  $P = 0.019$ , for retest on Day 1 vs. Day 2;  $t_{(14)} = -3.1$ ,  $P = 0.008$ , for pretest vs. retest on Day 2;  $F_{1.3,17.9} = 8.0$ ,  $P < 0.008$ , across the 3 tests). As the S-Deprivation group tended to exhibit a higher rate of express saccades already at the pretest ( $t_{(28)} = 1.9$ ,  $P = 0.063$ ), analyses were performed additionally on express rates controlling for baseline levels (i.e., on individual differences with reference to pretest performance). In these analyses, the increase in express saccades for the S-Deprivation group, compared with the Sleep group, was significant on Day 1 ( $t_{(28)} = 2.2$ ,  $P = 0.048$ ) and for Day 2 ( $t_{(28)} = 2.9$ ,  $P = 0.006$ ).

### Sleep-Dependent Learning of Express Saccades Persists 4 Weeks Later

Four weeks after the initial experimental session, Sleep and S-Deprivation groups were again tested following basically the same procedures, except that sleep and sleep deprivation conditions were exchanged (cross-over design): that is, subjects who previously slept after training stayed awake, and the subjects who had previously stayed awake now slept on the night after the training phase. In the subjects of the original S-Deprivation group, rates of express saccades at the pretest of this second session, although on average slightly (but nonsignificantly) lower than at retest on Day 2 of the first experimental session ( $t_{(11)} = 0.8$ ,  $P = 0.45$ ), were still significantly enhanced if compared with the initial pretest of the first session ( $t_{(11)} = -2.6$ ,  $P = 0.026$ , Fig. 1C). No such enhancement was seen in the original Sleep group ( $t_{(11)} = -0.6$ ,  $P = 0.59$ , for pretests of the first vs. second experimental session). Moreover, express saccade rates at retest on Day 2 of the initial experimental session predicted the rate of express saccades at the pretest 4 weeks later for both the original S-Deprivation group ( $r = 0.88$ ,  $P < 0.001$ ) and the original Sleep group ( $r = 0.75$ ,  $P = 0.005$ ).

Like in the initial experimental session, during this second session, subjects (of the original S-Deprivation group) who now slept regularly before all tests showed comparable rates of express saccades on these tests (all  $P > 0.39$ ). In contrast, the subjects (of the original Sleep group) who on this second session were deprived of sleep after training showed a distinct increase in express

saccade rates across pretest and retests reaching significance for the comparison between pretest and retest on Day 2 ( $P < 0.01$ , for Wilcoxon's signed rank test, Fig. 1C). A Friedman's test on the 3 testings of each group ( $P > 0.12$ ) as well as a respective Group  $\times$  Test ANOVA interaction effect (directly comparing pretest vs. retest on Day 2) failed to reach significance ( $F_{1,22} = 2.4$ ,  $P = 0.14$ ), which was probably partly due to the reduced sample size at this second session ( $n = 24$ , 6 subjects dropped out) and to the fact that data of the Sleep group were not normally distributed.

### Sleep and Regular Saccades

Sleep in the laboratory after saccade training was normal (Table 1). Polysomnographic data indicated that both the Sleep group and the S-Deprivation group (sleeping on the second session 4 weeks later) comprised homogenous samples of good sleepers. There were no differences in sleep parameters between the groups, and none of the sleep parameters on the posttraining night showed any significant correlation with express saccade rates on Day 1 (all  $P > 0.31$ ). Confirming our previous report (Gais et al. 2008), regular saccades (130–400 ms) increased in speed after nocturnal sleep compared with sleep deprivation in the first experimental session ( $F_{2,56} = 5.68$ ,  $P = 0.005$ , for Group  $\times$  Test interaction), with the Sleep group showing the greatest gains in response times from pretest to the retest on Day 1 ( $t_{(14)} = 3.4$ ,  $P = 0.004$ ; Day 1 vs. Day 2: n.s.), whereas the S-Deprivation group showed the greatest gains in response times from Day 1 to Day 2 ( $t_{(14)} = 4.4$ ,  $P < 0.001$ ). The respective mean  $\pm$  SEM response times for the Sleep group were  $199.8 \pm 7.6$  ms at the Pretest,  $185.7 \pm 4.7$  ms on Day 1, and  $190.0 \pm 6.1$  ms on Day 2. For the S-Deprivation group, response times were  $190.6 \pm 5.6$  ms at the Pretest,  $188.7 \pm 5.9$  ms on Day 1, and  $174.0 \pm 3.8$  ms on Day 2.

### Short Saccade Testing After Sleep Deprivation Is Sufficient to Trigger Sleep-dependent Gain in Express Saccades

The persistent increase in express saccades after sleep deprivation being even further enhanced after ensuing recovery sleep

**Table 1** Sleep parameters

Parameter	First session	Second session
TST [min]	460.0 $\pm$ 10.7	456.3 $\pm$ 8.4
Sleep onset [min]	4.02 $\pm$ 1.00	3.08 $\pm$ 1.09
SWS latency [min]	17.17 $\pm$ 2.34	20.88 $\pm$ 3.36
REM latency [min]	94.17 $\pm$ 6.77	90.83 $\pm$ 12.8
WASO [%]	3.08 $\pm$ 1.08	8.16 $\pm$ 4.25
Stage 1 [%]	9.47 $\pm$ 1.70	8.68 $\pm$ 1.49
Stage 2 [%]	41.03 $\pm$ 2.80	42.79 $\pm$ 3.68
Stage 3 [%]	10.51 $\pm$ 0.93	10.18 $\pm$ 0.90
Stage 4 [%]	12.00 $\pm$ 1.51	8.68 $\pm$ 2.05
REM sleep [%]	21.13 $\pm$ 1.29	19.01 $\pm$ 2.00
MT [%]	2.76 $\pm$ 0.31	2.05 $\pm$ 0.36
home TST [min]	569.33 $\pm$ 26.4	567.33 $\pm$ 28.3

Means  $\pm$  SEM total sleep time (TST), latencies of sleep onset (with reference lights off), of SWS and rapid eye movement (REM, with reference to sleep onset), as well as percentages (with reference to TST) of wake time after sleep onset (WASO), of non-REM sleep Stages 1–4, SWS (i.e., the sum of time in Stage 3 and 4 sleep), rapid eye movement (REM) sleep, and movement time (MT), for the first experimental session of the Sleep group ( $n = 15$ ) and the second experimental session of the initial S-Deprivation group ( $n = 12$ ) which was tested on the sleep condition 4 weeks later. The bottom line shows TST for recovery sleep after sleep deprivation, measured by actigraphy at the subject's home. There were no significant differences in sleep parameters between groups.

was an unexpected finding of the main experiment and suggests that sleep deprivation favors an oculomotor learning process that evolves during subsequent sleep. To examine the possible contributions of pretesting, presleep deprivation training, and retesting after nocturnal sleep deprivation, 3 additional groups of subjects were tested in conditions that systematically varied the S-Deprivation condition of the original main study (Fig. 2). 1) The No-Pretest/No-Train group was not presented with the task before nocturnal sleep deprivation but underwent the tests in the morning of Days 1 and 2. 2) The No-Train group was pretested before the nocturnal wake but did not receive any training before this night. 3) The No-Retest group was pretested and trained on the task before sleep deprivation but the retest on Day 1, under sleep-deprived conditions, was omitted.

Surprisingly, the No-Pretest/No-Train group, which was only subjected to a brief (240 trials) test on Day 1 after nocturnal sleep deprivation, showed an increase in the rate of express saccades on Day 2 after recovery sleep which was quite comparable with that seen in the original S-Deprivation group (Fig. 2,  $P > 0.73$ , for direct comparisons between these groups,  $t_{(14)} = -3.3$ ,  $P = 0.005$ , for Day 1 vs. Day 2 in the No-Train/No-Pretest group). The No-Train group showed systematic increases in the rate of express saccades across pretest and retests which were similar to that seen in the original S-Deprivation group (all  $P > 0.42$ , for direct comparisons between the groups), with the exception that the increase in express saccades at retest on Day 1 was practically missing ( $P > 0.56$ ). The increase in express saccades across recovery sleep in this group, however, was quite pronounced and significant in comparison to the pretest performance level ( $t_{(14)} = -3.1$ ,  $P = 0.007$ ) and to the retest on Day 1 ( $t_{(14)} = -2.6$ ,  $P = 0.02$ ;  $F_{2,28} = 5.9$ ,  $P = 0.004$  across all 3 tests). Importantly, the No-Retest group which performed saccade pretesting and training before the wake night, but was not subjected to a retest on Day 1 in sleep-deprived conditions, did not show any increase in the rate of express saccades when tested on Day 2 after recovery sleep ( $P > 0.9$ , for pretest vs. retest on Day 2). Performance differences on Day 2 of this group (with reference to the first testing of this group) were at a significantly lower level in comparison with all other groups, that is, the original S-Deprivation, the No-Pretest/No-Train group, and the No-Train group (all  $P < 0.03$ ). In combination these results reveal that brief practice of the saccade task (240 trials) during the test on Day 1 in sleep-deprived conditions is essential for a persistent sleep-dependent increase in express saccades to occur on Day 2.

### Learning During Sleep Deprivation Also Produces Increases in Very Fast Finger Motor Responses After Recovery Sleep

We asked whether the sequence of a brief training in conditions of sleep deprivation followed by recovery sleep can also accelerate responses in other motor systems. To this end, in a supplementary study 2 groups of subjects, a Sleep and an S-Deprivation group were tested on a simple 2-choice finger motor reaction task sharing basic features of the oculomotor task of the main study. Like the No-Pretest/No-Train groups of the main study, subjects of both the Sleep and S-Deprivation group performed the finger motor task the first time in the morning of Day 1 after a night of regular sleep or sleep deprivation, respectively, without any pretesting or training before this night (Fig. 3A). The second test took place 24 h later (Day 2) after either regular sleep and recovery sleep. Finger motor responses with latencies  $>275$  ms were defined as regular finger presses; responses with latencies between 150 and 275 ms as very fast "express-like finger responses."

In the S-Deprivation group, the percentage of very fast finger responses increased from Day 1 (after sleep deprivation) to Day 2 (after recovery sleep) on average by ~5%, that is, from  $3.0 \pm 0.8\%$  to  $7.9 \pm 1.8\%$  ( $t_{(9)} = -3.6$ ,  $P = 0.006$ , Fig. 3B). In the Sleep group, the corresponding increase in very fast finger responses was marginal (0.6%) and failed to reach significance (Day 1:  $1.5 \pm 0.3\%$ , Day 2:  $2.1 \pm 0.6\%$ ,  $P = 0.39$ ;  $F_{1,18} = 8.5$ ,  $P = 0.009$ , for Group  $\times$  Test interaction). Regular responses were also faster on Day 2 than on Day 1 (by ~30 ms) in the S-Deprivation group ( $355.9 \pm 4.8$  vs.  $384.9 \pm 9.1$  ms,  $t_{(9)} = 4.3$ ,  $P = 0.002$ ) but not in the Sleep group ( $381.9 \pm 8.3$  vs.  $387.7 \pm 7.1$ ,  $P = 0.39$ ;  $F_{1,18} = 6.2$ ,  $P = 0.023$  for Group  $\times$  Test interaction). Percentages of express finger responses on Day 1 were slightly higher in the S-Deprivation than in the Sleep group ( $t_{(18)} = 1.8$ ,  $P = 0.094$ ). Latencies of regular response on Day 1 were comparable between the groups ( $t_{(18)} = 0.2$ ,  $P = 0.81$ ). There were also no significant time-on-task effects across the 4 blocks on reaction times ( $P > 0.9$ , Fig. 3C).

## Discussion

Sleep has been shown to benefit very different kinds of memory including procedural memory for visual discrimination, motor, and oculomotor skills (Karni et al. 1994; Gais et al. 2000; Walker et al. 2003; Walker 2005; Albouy et al. 2006; Albouy et al. 2008; Gais et al. 2008). Contrasting with these findings, here sleep after training on a standard prosaccade gap task did not enhance the occurrence of very fast saccades, that is, express saccades, in comparison with a posttraining period of nocturnal wakefulness. Importantly, however, express saccade rates were enhanced in the retest after the nocturnal vigil, and only recovery sleep after this retest performed in sleep-deprived conditions produced a significant overnight gain in express saccades, as revealed at the second retest (on Day 2). This gain in express saccades was long lasting and still significant 4 weeks later (in the beginning of the second session). Additional experiments confirmed that it is indeed the short period of prosaccade practice during the retest in sleep-deprived conditions that plays a causal role for the overnight gain in express saccades across recovery sleep. Also, we showed a similar increase across recovery sleep in very fast “express-like” finger press responses after a brief training in sleep-deprived conditions, suggesting that the sequence of training in sleep-deprived conditions followed by recovery sleep can be used to produce very fast responses also in other motor systems. We postulate that sleep deprivation relieves motor behavior from prefrontal cortical inhibition. Short practice in this sleep-deprived condition apparently suffices to trigger sleep-dependent plastic synaptic changes that consolidate response pathways bypassing prefrontal cortical suppressive control.

Why did sleep following saccade training not produce the expected overnight gain in express saccades? One factor could have been the presleep rate of express saccades in the Sleep group which tended to be lower than in the other groups, although subjects were randomly assigned to the groups. We can only speculate about the origin of this difference which might reflect nonspecific effects like anticipations regarding the following night (to be spent asleep or awake) or pure chance. However, these differences were unexpected, statistically not significant, and most importantly, the central study results remained the same after controlling data for this baseline difference. Nevertheless, overnight gains in motor skill indeed have been found to strongly depend on the presleep performance level, with the most pronounced overnight gains induced at an intermediate skill level (Hauptmann et al. 2005; Albouy et al. 2008; Stickgold 2009; Wilhelm et al. 2012). Also, in line with this reasoning the

S-Deprivation group showed significant increases across recovery sleep, as the level of express saccades in this group before recovery sleep was indeed distinctly higher than that during the pretest of the Sleep group. Finally, the Sleep group did exhibit a sleep-associated increase in express saccade rates in the second session after express saccade rates were elevated due to prior sleep deprivation. On the other side, compared with performance of the Sleep group, reaction times in the 2-choice finger motor task in the S-Deprivation group were distinctly faster only after the night of recovery sleep, whereas reaction times at the initial training were closely comparable between groups (Fig. 3). This pattern suggests that gains in very fast responses across recovery sleep can basically evolve also in the absence of an immediate speeding of responses in sleep-deprived conditions.

While the present data do not allow to decide whether an increase in basal rates of express saccades itself is sufficient to provoke sleep-dependent gains in express saccades, the data demonstrate that such gains occur when express saccade levels are enhanced as a consequence of deprived sleep. Indeed, our findings confirm that sleep deprivation enhances the production of express saccades (Bocca and Denise 2006), and this enhancement was independent of whether subjects had or had not extensively trained prosaccades on the evening before nocturnal sleep deprivation. Our control experiments on the effects of sleep deprivation revealed the No-Retest group to be the only one that did not show an increase in express saccade levels across ensuing recovery sleep, and this group was also the only one that was not retested on the day after the nocturnal vigil. This finding rules out sleep deprivation as the only factor enabling overnight gains in express saccades during recovery sleep in a nonspecific manner. On the contrary, the finding identifies brief saccade practicing (i.e., 240 trials) during the test phase as a factor causally contributing to the overnight gain. How sleep deprivation primes the oculomotor system to enable enduring sleep-dependent enhancements in express saccades, and whether this perhaps involves activation of stress systems (Schwabe and Wolf 2013), is in need of further experimentation.

Although with the 2-choice finger motor task we have provided evidence that the sequence of training in sleep-deprived conditions followed by recovery sleep cannot only be used to increase the rate of express saccades but also of very fast finger responses, we caution against a premature generalization of this phenomenon across motor domains. Indeed, reaction times in the delayed 2-choice finger motor task normally do not show the bimodal distribution that is typically observed for saccades in the prosaccade gap paradigm (Ross and Ross 1981; Fischer et al. 1984; Bekkering et al. 1996). Also, to the best of our knowledge, there is no evidence for a distinct neuronal system involved in very fast compared with regular finger reaction times in such tasks, unless the response is incorrect. However, incorrect or grossly inaccurate responses on both the 2-choice finger motor task and the prosaccade gap paradigm, respectively, were very rare and excluded from the analyses. For safe generalization across motor domains, the comparability of specific task features appears to also be of importance, such as to what extent the production of very fast responses depends on the gap between fixation and target stimulus and on the complexity of the decision associated with the target stimulus (Mayfrank et al. 1986; Iwasaki 1990; Fischer and Weber 1993; Machado-Pinheiro et al. 1998; Machado-Pinheiro et al. 2003).

Our data indicate that practicing motor tasks in sleep-deprived conditions promotes consolidation processes during ensuing recovery sleep that specifically favor the generation of very fast “express” responses on the task. We can only speculate

about the underlying neural mechanisms of this phenomenon. Two major streams are discerned that interactively control saccades: a posterior one that mainly involves the visual cortex (V1, V2) and lateral intraparietal sulcus and reaches the brainstem oculomotor nuclei via the superior colliculus, and an anterior one that involves the frontal and medial eye fields and directly accesses brainstem oculomotor centers (Tinsley and Everling 2002; Schiller and Tehovnik 2005; Everling and Johnston 2013). Express saccades are generated via the posterior stream. Unlike regular saccades, their execution critically relies on the superior colliculus. Moreover, neurons in the lateral intraparietal cortex selectively increase activity during express saccades (Chen et al. 2013). Lesions to the anterior processing stream, specifically to the frontal eye fields, appear to primarily interfere with target selection and thereby indirectly modulate express saccade rates without suppressing them (Schiller et al. 1987; Rivaud et al. 1994). The major suppressive influence on express saccades originates from the lateral prefrontal cortex, lesions of which markedly increase their production, leaving regular saccades unaffected (Braun et al. 1992; Müri et al. 1999). Whether this suppressive control reflects a top-down neuronal inhibitory control over the superior colliculus or a regulatory routing of different visual processing pathways is controversial, as the major influence of lateral prefrontal cortex on the oculomotor system seems to be excitatory in nature (Guan et al. 2012; Everling and Johnston 2013; Johnston et al. 2014). Regardless of this issue, in this model the lateral prefrontal cortex appears to be the candidate structure conveying the disinhibiting influence of sleep deprivation on express saccade production. Prefrontal inhibitory control over motor responses is well known to be highly sensitive to the detrimental effects of sleep deprivation (Muzur et al. 2002; Griffith and Rosbash 2008; Goel et al. 2009). Thus, sleep deprivation by impairing lateral prefrontal inhibitory control might enable learning of direct routing of visual information to motor output formations through the posterior stream, bypassing prefrontal inhibitory circuitry. This explanation is, of course, tentative as direct evidence for this mechanism, for example, by experimentally inactivating respective lateral prefrontal neuron networks, is lacking.

Inhibitory behavioral control belongs to the cardinal executive functions mediated by the prefrontal cortex (Munakata et al. 2011; Bari and Robbins 2013), and there is evidence from studies of go/nogo tasks and fear extinction learning that sleep might support such inhibitory function (Hussaini et al. 2009; Datta and O'Malley 2013; Borquez et al. 2014). However, whereas those previous studies demonstrate a strengthening of inhibitory control by sleep, this study shows that sleep can help learn to diminish inhibitory control. Indeed, this finding appears to stand in contrast with concepts assuming that sleep, specifically slow wave sleep (SWS), preferentially supports consolidation of memories involving the prefrontal-hippocampal system during encoding (Marshall and Born 2007; Inostroza and Born 2013). However, it could be argued that, rather than SWS, it is mainly a function of REM sleep to promote memory for fast automatized behaviors that occur in the absence of executive inhibitory control (Plihal and Born 1997). Also, reducing behavioral inhibition during prosaccade performance does not necessarily imply a complete disengagement of prefrontal control, but the prefrontal cortex might still remain involved in an attentional routing of task stimuli. Beyond these open questions, the astonishing findings that the sequence of brief practice of simple motor responses in sleep-deprived conditions followed by recovery sleep produces a speeding of the practiced response calls for testing possible beneficial applications, especially since the speeding

effect can be quite long lasting, as shown here for express saccades. For example, the procedure might be applicable to speed skills relevant for expert performances of certain sports or for visual monitoring of safety relevant systems, that is, where extremely quick responses without a crucial loss of accuracy are a “wanted” effect. From an evolutionary perspective, excluding frontal cortical control from saccade generation might aid to recognize and escape certain dangers more quickly (Dorris et al. 1997). Yet, express saccades and very fast motor responses basically represent an impulsive behavior that can be beneficial in some conditions but can also be detrimental and then represent an “unwanted” effect. In this regard, our findings suggest that repeated instances of sleep deprivation and sleep curtailment also bear the risk of developing unwanted trait-like patterns of impulsive behaviors escaping executive control, as observed in disorders like the attention deficit hyperactivity syndrome and substance abuse.

## Supplementary Material

Supplementary material can be found at <http://www.cercor.oxfordjournals.org/online>.

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## Notes

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