



## Research report

# Evidence for two distinct sleep-related long-term memory consolidation processes



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## ABSTRACT

Numerous studies examine the effect of a night's sleep on memory consolidation, but few go beyond this short time-scale to test long-lasting effects of sleep on memory. We investigated long-term effects of sleep on typical memory tasks. During the hours following learning, participants slept or stayed awake. We compared recall performance between wake and sleep conditions after delays of up to 6 days. Performance develops in two distinct ways. Word pair, syllable, and motor sequence learning tasks benefit from sleep during the first day after encoding, when compared with daytime or nighttime wakefulness. However, performance in the wake conditions recovers after another night of sleep, so that we observe no lasting effect of sleep. Sleep deprivation before recall does not impair performance. Thus, fatigue cannot adequately explain the lack of long-term effects. We suggest that the hippocampus might serve as a buffer during the retention interval, and consolidation occurs during delayed sleep. In contrast, a non-hippocampal mirror-tracing task benefits significantly from sleep, even when tested after a 4-day delay including recovery sleep. This indicates a dissociation between two sleep-related consolidation mechanisms, which could rely on distinct neuronal processes.

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## 1. Introduction

Sleep represents an important part of daily life. Whereas early theories of sleep function emphasized mainly recuperation and energy conservation, more recently, its role in cognitive performance has come into focus. Astonishingly, only few

aspects of cognition have proven to be consistently affected by sleep, the most prominent of which are probably sustained attention and memory. Sustained attention is impaired by lack of sleep (Killgore, 2010); memory performance is enhanced by sleep (Diekelmann & Born, 2010). Systems memory consolidation is one mechanism by which sleep can support memory formation. By reactivation and consequent

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strengthening, neuronal traces of newly learned memories are thought to be integrated into existing memory networks and made more durable (Rasch, Büchel, Gais, & Born, 2007; Stickgold & Walker, 2013). Reactivation is supposed to originate in the hippocampus. Hippocampal reactivation then leads reactivation in neocortical or striatal areas (Ji & Wilson, 2007; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009). This mechanism can therefore be assumed to underlie mainly hippocampus-dependent memory (Inostroza & Born, 2013). However, it has been proposed to also mediate consolidation of some procedural tasks with hippocampal contributions, possibly linked to explicit aspects of these tasks (Cohen, Pascual-Leone, Press, & Robertson, 2005; Geyer, Mueller, Assumpcao, & Gais, 2013; Robertson, Pascual-Leone, & Press, 2004; Schönauer, Geisler, & Gais, 2014; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). Reactivation of learning-related neural activity during sleep can be observed not only in the hippocampus, but in many of the regions involved in learning (Maquet et al., 2000). Whether consolidation in all memory systems relies on the same neuronal processes is still unclear.

When considering typical experimental designs used to study the effects of sleep on declarative memory, large gaps in our knowledge become apparent. Mostly, participants have to learn some kind of material before a period of sleep or wakefulness, and they are asked to retrieve this material afterward. The duration of the retention interval usually lies between 1 and 24 h. Often, retention periods filled with sleep are directly compared with periods filled with wakefulness. While appropriate for many research questions, some central positions cannot be analyzed using this experimental design. First, it is difficult to distinguish between effects of sleep on consolidation of previously learned memory and effects of sleep on following memory retrieval: memory retrieval may be impaired because of fatigue after a night of sleep deprivation. Confounds include effects of prior sleep on following memory encoding and circadian factors when comparing morning–evening versus evening–morning settings. Finally, because many studies use short retention intervals, only little is known about long-term effects of sleep on memory. Examining long-term effects of sleep on memory can give a more comprehensive view of the extended consolidation process and its neuronal dynamics. It can thus shed further light on the specific mechanisms that mediate consolidation in different memory systems.

As mentioned above, most studies on declarative memory test performance within the first 24 h after learning. Only occasionally, experimental designs include recovery sleep, mainly with the intention to avoid effects of acute fatigue in designs using sleep deprivation. Just a few studies systematically explore longer retention intervals after sleep deprivation, and most of these are quite old (Rasch & Born, 2013). The longest interval tested for non-emotional declarative memory – six days between learning and recall – was investigated by Graves (1937). She tested whether learning in the evening (sleeping after learning) or learning in the morning (staying awake after learning) influenced retention after 24, 48, 72, 96 or 144 h. She used nonsense syllables as learning material and the savings method as performance measure, i.e., the reduction in the number of relearning repetitions required for

perfect list reproduction. Graves found a long-range effect of sleep on syllable recall developing after 72 h, but none before that. Apart from being only a single-participant study – testing the author herself – and not using a standardized method of presentation, this study confounds circadian effects with effects of sleep. The finding was replicated by another study, which used a very similar study design and the same task, but employed a larger group of participants and better-controlled experimental conditions (Richardson & Gough, 1963). These authors also find a similar delay in the onset of effects. They find no difference between the sleep and wake conditions after 24 and 48 h, but only after 144 h. These results stand in contrast to a large body of recent literature which stresses immediate effects of sleep on memory performance (Diekelmann & Born, 2010).

Apart from these older findings, some more recent studies examined memory performance following consolidation in sleep or wakefulness after 2- or 3-day intervals. Gais et al. (2007) saw a significant sleep effect on word-pair learning after a 44-h retention interval comprising two nights of sleep or one night of sleep deprivation and one night of recovery sleep. In a comparable study design, Gais, Lucas, and Born (2006) found a positive effect of sleep on foreign language vocabulary after a 48-h interval containing two undisturbed nights of sleep or one night of sleep deprivation and one night of recovery sleep. However, no significant effect of sleep versus sleep deprivation on behavioral performance was found after 3 days for spatial memory in a virtual maze task (Orban et al., 2006). Sterpenich et al. (2007) tested recognition in a remember/know paradigm and found a significant positive effect of sleep on recollection of neutral and emotionally positive images when comparing three nights of sleep with one night of sleep deprivation and two recovery nights. In the same study, emotionally negative material did not show long-term benefits of sleep. Smith (1995) briefly reports of a study that did not find effects of sleep deprivation after learning on word recognition and figure reproduction one week later.

Regarding retention intervals longer than a few days, evidence is exceptionally scarce. There are several fMRI studies that assessed performance after 6-months delays, demonstrating clear differences in recall-related brain activity, but finding no significant differences in performance between participants who slept or were sleep-deprived after learning (Gais et al., 2007; Rauchs et al., 2008; Sterpenich et al., 2009). Only one study reports that three hours of sleep after learning dramatically increase recognition memory for emotional texts in an unannounced test four years after the original experiments (Wagner, Hallschmid, Rasch, & Born, 2006). In the same experiment, non-emotional texts did not benefit from sleep.

In the domain of non-declarative memory, effects induced by one night of sleep deprivation can be long lasting: participants will not benefit from practicing a visual discrimination task if they are sleep deprived for one single night after learning the task, even if performance is measured after several recovery nights. The benefit of sleep, on the other hand, persists even after a week (Stickgold, James, & Hobson, 2000). Similarly, a motor adaptation task shows sleep-induced improvements three days after a night of sleep or sleep

deprivation (Maquet, Schwartz, Passingham, & Frith, 2003). Also, Smith (1995) reports that memory in a number of procedural tasks was impaired one week after REM sleep deprivation. Together, there is some evidence for a long-lasting effect of sleep on procedural and emotional memory, whereas findings for neutral declarative memory are mixed. The number of studies investigating long-term effects of sleep is very small considering the total number of publications on this topic, and results remain inconclusive as to the existence of long-lasting effects of sleep.

In two separate studies, we investigate whether sleep after learning, compared with sleep deprivation or day-wake periods of equal length, shows a lasting beneficial effect on memory performance. We tested retention intervals of up to six days. The first experiment tested verbal word pair learning and a procedural mirror-tracing task. We seek to answer three questions. First, is there an effect of sleep after learning that is it still detectable after four nights? We know from previous studies using the same material that an effect should be observed after one night. Only little data is available on long-term effects, however. Results on declarative memory are inconsistent when going beyond a timescale of two days from learning. Given findings on tasks with strong procedural components (Maquet et al., 2003; Smith, 1995; Stickgold et al., 2000), we expect clear long-term effects for mirror-tracing performance. Second, because previous experiments often tested directly after sleep or wakefulness, some effects of sleep can be interpreted either as effects of sleep on memory consolidation or as effects of sleep deprivation on following memory recall. Therefore, we introduce an additional condition that controls for effects of sleep deprivation before memory recall. Third, we used semantically related word pairs as well as unrelated word pairs as learning material because in previous studies, it remained open which type of material preferably benefits from sleep. While in an early study by Plihal and Born (1997) and a number of experiments following the same experimental procedures related word pairs benefitted from reactivation in sleep, a newer study by Payne et al. (2012) shows that unrelated, but not related word pairs are remembered better over sleep than wakefulness. The second experiment was based on an older study that described an effect of sleep that not only persisted but increased over time (Richardson & Gough, 1963). We used the same nonsense syllable material and procedure as that study, testing different time intervals to investigate how effects develop. Furthermore, we tested performance on a finger sequence tapping task. Additionally, because Richardson and Gough (1963) used a night-sleep/day-wake design and did not control for circadian effects, we added a night-wake control condition.

## 2. Methods and results

### 2.1. Experiment 1

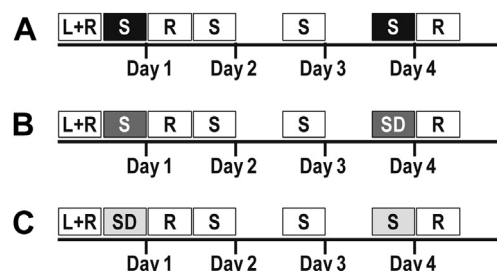
#### 2.1.1. Methods

2.1.1.1. GENERAL PROCEDURE. 21 healthy, young participants [aged  $24.3 \pm 2.7$  years (mean  $\pm$  SD)] participated in three experimental conditions. They were non-smokers, regular

sleepers, and did not take any regular medication except contraceptives. They were not allowed to use caffeine 12 h before and during the experiment. Each condition consisted of one learning and two testing sessions. In the first session of each condition, which took place in the evening, 2 h before bedtime, participants learned word lists and practiced a mirror-tracing task (Plihal & Born, 1997). During the following night, they either slept or stayed awake, depending on the experimental condition. In the morning after this first night, at 7 a.m., memory was tested. For the next two nights, participants slept normally. During the fourth night, participants again slept or stayed awake and were tested in the following morning. Together, over the three conditions, participants were once sleep deprived after learning, once sleep deprived before testing, and once allowed to sleep during all four nights (see Fig. 1). All participants gave informed consent before participating in the study.

2.1.1.2. TASKS. The first task was a paired-associate word list learning task that consisted of 4 lists of 20 pairs. Two lists contained semantically related pairs (e.g., breakfast – crumb, insect – horsefly), the other two contained unrelated pairs (e.g., volcano – gravy, fork – flower). Participants were presented with 4 pages of 5 pairs for 15 sec each. After initial stimulus presentation, we showed the first word of each pair in random order, and they had to name the matching word aloud. If less than 70% of correct answers were given on one of the four lists, presentation of this list was repeated until that threshold was reached. This procedure ensured that the same learning criterion was reached for all lists. Participants needed on average  $1.1 \pm .2$  repetitions for related pairs and  $1.8 \pm .5$  repetitions for unrelated pairs ( $p < .001$ ). Recall was tested twice, once after the first night, once after the fourth night. Each time, we tested half of the material, i.e., one related and one unrelated list.

We additionally tested procedural memory using a mirror-tracing task. Here, participants had to trace a figure while seeing their hand, the stylus and the figure only in a mirror. Tracing speed, number of times the stylus moved off the figure (errors) and time the stylus stayed outside the figures (error time) were measured electronically. To avoid fast within-



**Fig. 1 – Design of Experiment 1.** Subjects participated in three experimental conditions. Each condition consisted of one learning session in the evening including initial performance assessment (L + R), and two testing sessions (R) in the mornings of day 1 and day 4. Participants were allowed to sleep (S) during all four nights in condition A, were sleep deprived (SD) before delayed testing on day 4 in condition B, or after learning on day 1 in condition C.

session adaptation, participants first had to practice the task on a simple star figure until they could complete this figure in less than 60 sec and with less than 9 errors. Then they had to trace one of the three actual figures as fast as possible. In each condition, a different figure was used. The figures differed in the preferential direction and shape of angles. Participants had to stay within the boundaries of the lines, which were 1 cm wide. As it is common practice in numerous studies, we tested two tasks in each experiment (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006; Plihal & Born, 1997; Smith, 1995). According to Brown and Robertson (2007), it is possible that the second task interferes with the consolidation of the first for subjects in a wake condition. This can enlarge the effect of sleep compared to wakefulness, similar to what has been found for interference within declarative memory (Ellenbogen et al., 2006).

In a third task, long-term memory access was tested. Here, participants had to name as many female first names and male first names starting with a certain letter. Letters were selected to have similar frequency in lists of German first names (E, S, L for female names, B, J, M for male names). There was no speed component, but participants were told to finish within about 5 min.

**2.1.1.3. SLEEP.** Participants slept at home. Sleep duration was recorded by the participant with a sleep log and confirmed by actimetric recordings. In nights during which participants had to stay awake, participants stayed in the laboratory under the supervision of the experimenter and played board games. Participants were allowed to leave the lab after 8 a.m. in the morning to follow their usual daily activity. Daytime naps were not allowed and activity was monitored using actimetry.

**2.1.1.4. STATISTICAL ANALYSES.** The main analysis is based on a mixed general linear model with the within-subject factors delay (1 day, 4 days) and condition (sleep on night 1, sleep deprivation on day 1, sleep deprivation before day 4 recall). Analysis was done in SPSS 21. Note that degrees of freedom can be decimals in mixed models analyses. All tests are based on a two-sided significance level of .05. All values are given as mean  $\pm$  s.e.m.

## 2.1.2. Results

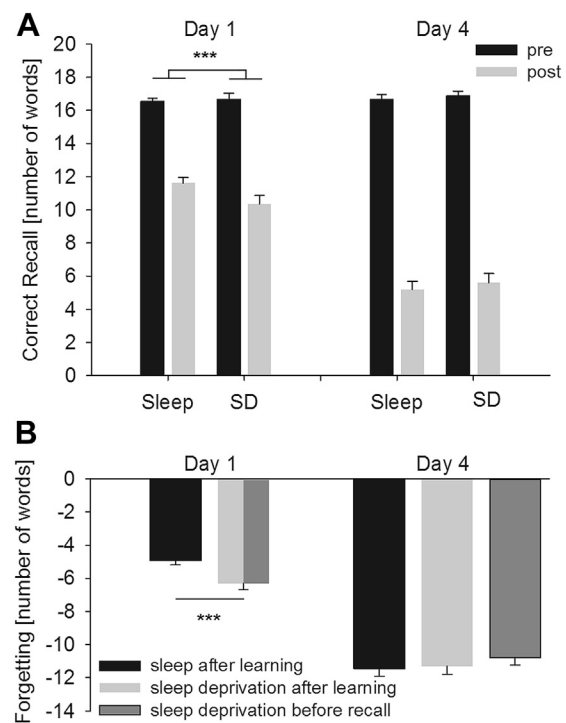
**2.1.2.1. DECLARATIVE MEMORY.** We first asked whether sleep after learning affects retrieval of word pair memory 1 or 4 days afterward. Whereas there was a significant difference in retention of word pairs on day 1 between sleep (S) and sleep deprivation (SD;  $F_{1,34.0} = 16.8$ ,  $p < .001$  for interaction pre/post  $\times$  S/SD), we no longer observed this difference on day 4 after S or SD ( $F_{1,34.7} = .65$ ,  $p = .43$  for interaction pre/post  $\times$  S/SD). The interaction between delay (day 1, day 4) and sleep (S, SD) is significant, confirming that measurements actually differ between time points and sleep affects early more than late long-term memory performance ( $F_{1,37.6} = 32.9$ ,  $p < .001$ ; see Fig. 2). SD before recall has no significant effect on memory performance. If anything, participants in the SD condition were slightly better than in the other two conditions ( $F_{1,32.0} = 2.4$ ,  $p > .1$ ).

Word pairs with a semantic relation are usually remembered more easily than word pairs with no such relation. To

test whether sleep affects semantically related and semantically unrelated word pairs differently, we compared both types of material after S and SD in the 1-day and the 4-day retention conditions. On day 4, no significant interaction between S versus SD deprivation and semantically related versus unrelated word pairs was found ( $F_{1,40.8} = .51$ ,  $p = .48$ ), as could be expected from the missing effect of sleep per se. Interestingly however, on day 1, the benefit of semantic relation (difference in memory performance between semantically related and unrelated items) was completely absent after sleep deprivation. Numerically, unrelated pairs were even remembered better ( $F_{1,33.4} = 2.2$ ,  $p = .15$ ). A comparison of semantically related versus unrelated word pairs between S and SD was significant on day 1 ( $F_{1,38.5} = 9.5$ ,  $p = .004$ ; see Fig. 3), showing that only semantically related word pairs gained from sleep.

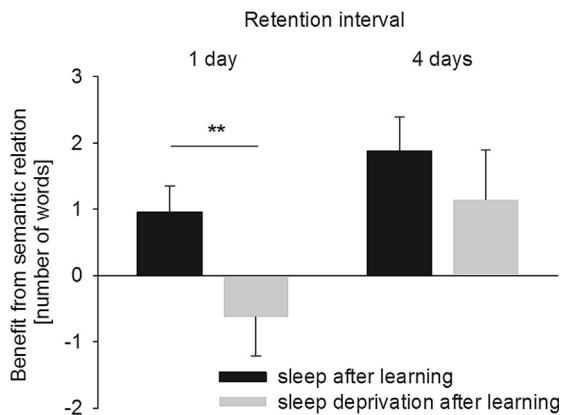
An effect of sleep deprivation on word fluency was not found in the data. Production of names was similar after S and SD nights (S:  $15.3 \pm .9$  names, SD:  $16.1 \pm 1.1$ ,  $F_{1,39.7} = .90$ ,  $p = .35$ ).

**2.1.2.2. PROCEDURAL MEMORY.** In the procedural mirror-tracing task, results differed clearly from word pair memory. Here, significant effects were seen both on day 1 and on day 4.



**Fig. 2 – Memory performance for word pairs after retention intervals of 1 and 4 days. A. Absolute values for word pair recall immediately after learning (pre) and after the retention interval (post). B. Forgetting of word pairs over the retention intervals. A significant positive effect of sleep can only be seen after the first night. The observed effect does not seem to be attributable to fatigue induced by sleep deprivation because sleep deprivation during the night before recall on day 4 has no effect on memory performance.**





**Fig. 3 – Semantically related word pairs benefit more from sleep than semantically unrelated words. This effect can only be seen on the first day after sleep deprivation, as no significant effect of sleep exists after four days. Benefit from semantic relation is calculated as the difference in memory performance between semantically related and unrelated items.**

Consolidation, as measured by the reduction in the number of errors between learning and testing, was significantly stronger after S than SD (day 1:  $F_{1,20} = 5.2$ ,  $p = .03$ ; day 4:  $F_{1,20} = 7.7$ ,  $p = .01$ ; see Fig. 4). Similarly, reduction in error time was significantly larger after S than SD (day 1:  $F_{1,20} = 22.2$ ,  $p < .001$ ; day 4:  $F_{1,20} = 7.1$ ,  $p = .01$ ). Improvement in tracing speed was also numerically higher after S than SD, but not significantly so (day 1:  $F_{1,20} = 1.0$ ,  $p = .33$ ; day 4:  $F_{1,20} = 1.0$ ,  $p = .33$ ). For all

three measures, interactions between S/SD and day 1/day 4 were not significant (all  $p > .46$ ). In this procedural task, however, SD before testing on day 4 has a small, non-significant detrimental effect (see Fig. 4). Speed and error performance differ significantly neither from S nor from SD (all  $p > .1$ ). Therefore, a detrimental effect of fatigue on performance cannot be excluded in any experiment in which participants were sleep deprived directly before performance testing.

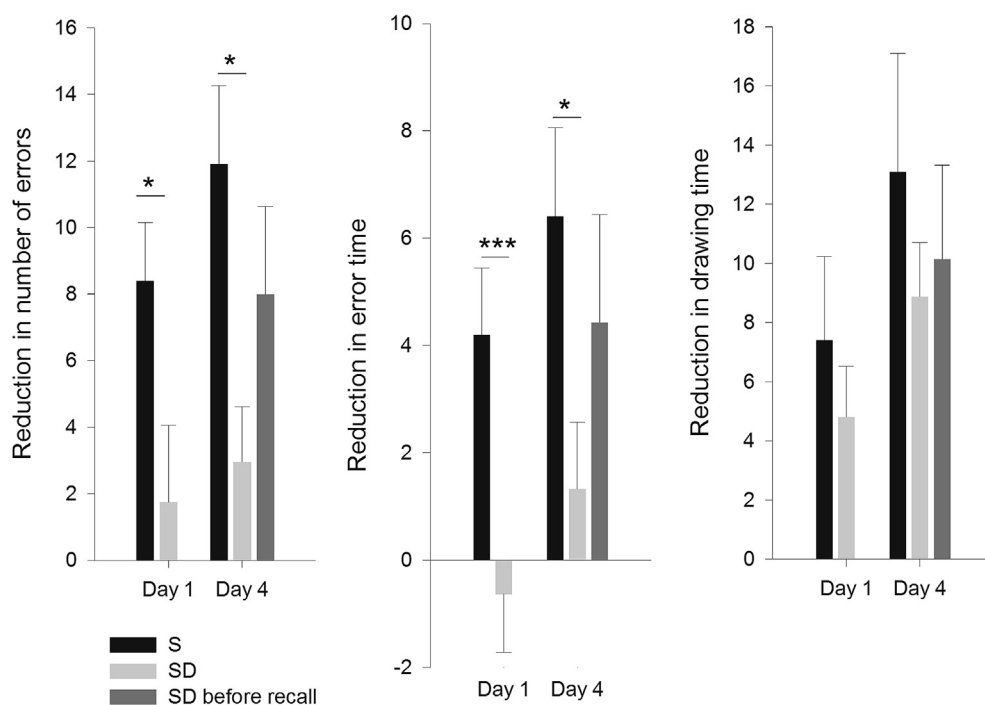
**2.1.2.3. SLEEP.** Sleep during the four nights between learning and retesting was documented in sleep logs and verified by actimetry. Overall, participants slept 7 h 40 min ( $\pm 7$  min) during these nights.

## 2.2. Experiment 2

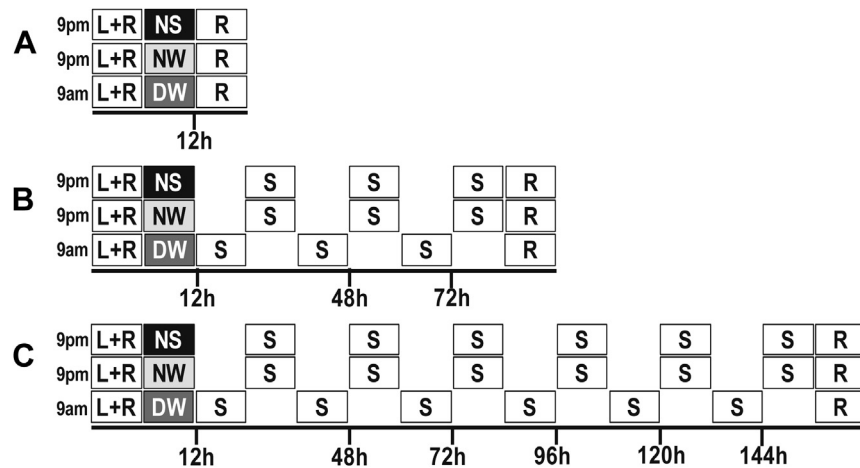
### 2.2.1. Methods

**2.2.1.1. GENERAL PROCEDURE.** 36 healthy, young native German speakers (aged  $22.5 \pm 3.6$  years) were assigned to one of three experimental groups, each comprising of three experimental conditions. Each condition consisted of a learning session and a testing session. Depending on the condition, learning took place at 9 a.m. before a day of wakefulness (DW), at 9 p.m. before a night of sleep (NS), or at 9 p.m. before a night of sleep deprivation (NW). Testing took place 12 h, 72 h or 144 h after learning for the three groups, respectively (see Fig. 5). Order of conditions was fully balanced across groups and subjects.

Potential participants with sleep disorders were not admitted to the study. Only subjects were allowed to participate who had a regular sleep rhythm (e.g., no sleep pathologies, no crossing of time zone borders, no shift work, and no



**Fig. 4 – Results of the mirror-tracing task. Significant improvements from sleep after training can be seen both on day 1 and on day 4. Thus, the benefit from sleep seems to be persistent. Sleep deprivation before testing has no significant effects, although the values lie slightly below those of the sleep condition.**



**Fig. 5 – Design of Experiment 2.** Subjects were assigned to three experimental groups (A, B, C). All subjects had to participate in three different experimental conditions, consisting of a learning session including initial performance assessment (L + R) and delayed testing (R). Depending on the condition, learning took place at 9 a.m. before a day of wakefulness (DW), at 9 p.m. before a night of sleep (NS), or at 9 p.m. before a night of sleep deprivation (NW). Group A was tested 12 h after learning in all three conditions, group B after 72 h, and group C after 144 h.

other sleep restrictions). Participants were asked not to use caffeine or centrally active medication on the days of the experiments. All gave informed consent before participating in the study.

**2.2.1.2. TASKS.** First, participants learned a list of 10 meaningless consonant-vocal-consonant (CVC) syllables until they were able to reproduce the whole list without errors three times in a row (Richardson & Gough, 1963). Syllables were randomly chosen from a list of syllables that had been rated to be non-meaningful and of medium difficulty in a pre-test. All 10 syllables were presented in a fixed order one after another for 1.6 sec each. Then, learning was tested in a typed free recall procedure. If list reproduction was not perfect, presentation started again from the beginning. The number of presentations until full recall marked initial performance. Later, during testing, participants were first asked to recall as many syllables as possible (free recall score). Additionally, a relearning score was obtained as the number of presentations required until the participant could again reproduce the list without errors three times in a row. A saving score was calculated as the percentage of trials saved during retesting compared with initial learning.

In addition, participants performed a simple sequential finger tapping task of five elements with the fingers of their non-dominant hand (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Three sequences were assigned to the three conditions (4-2-3-1-4, 2-4-1-3-2, 2-3-1-4-2). The sequences were balanced across conditions and groups. Participants were instructed to follow the sequence as fast and as accurately as possible. The sequence was displayed as a string of numbers on a computer screen; position within the sequence was indicated by asterisks below. The number of correct sequences (speed) and the number of errors (accuracy) per 30 sec was calculated. Learning consisted of 12 trials of 30 sec. The last three trials were used to determine initial learning performance. Testing after sleep or wakefulness consisted of

three trials of 30 sec as well. After each trial, there was a pause of 30 sec.

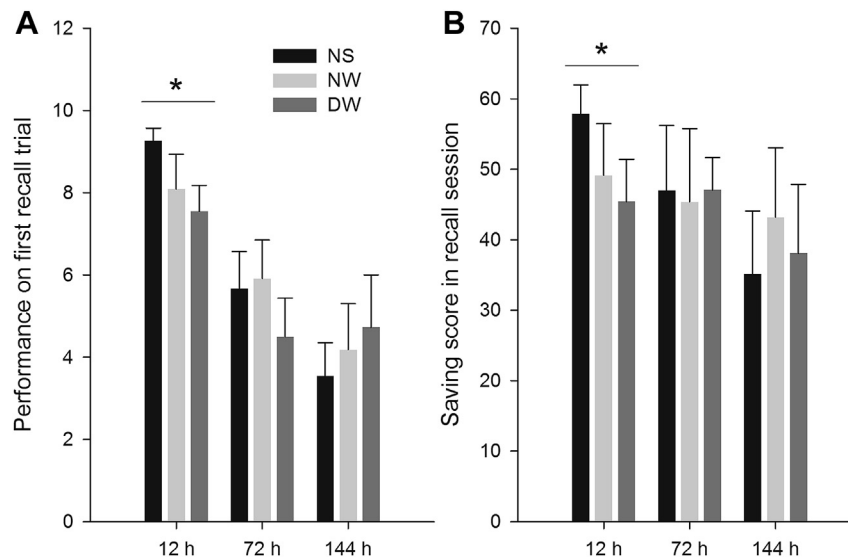
Verbal and non-verbal IQ was measured with the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl, 2005) and the Zahlen-Verbindungs-Test (ZVT) (Oswald & Roth, 1987), respectively, two German standard test batteries. There were no noticeable results (average verbal IQ in MWT:  $109 \pm 2$ ; average numerical speed IQ in ZVT:  $115 \pm 2.8$ ).

**2.2.1.3. SLEEP.** Participants filled out sleep logs during the five days prior to the experiments. During sleep deprivation nights, participants were playing games or watching non-arousing movies under constant supervision of an experimenter. For all periods between learning and testing during which the participant was not under direct supervision of the experimenter, a sleep log had to be kept, and activity was controlled by actimetry.

**2.2.1.4. STATISTICAL ANALYSES.** Analyses were done in SPSS 21, based on a mixed general linear model with one within-subject factor (condition: night sleep, night wake, day wake) and one between-subject factor (delay: 12 h, 72 h, 144 h). Note that degrees of freedom can be decimals in mixed models analyses. All tests are based on a two-sided significance level of  $\alpha = .05$ . All values are given as mean  $\pm$  s.e.m.

## 2.2.2. Results

**2.2.2.1. DECLARATIVE MEMORY.** First, we tested whether declarative memory recall benefitted from sleep after learning, and whether such an effect would be detectable for longer periods of time. We found a significant effect of condition (NS, NW, DW) on the number of syllables remembered in the 12-h group ( $F_{1,10} = 8.7, p = .01$ ; see Fig. 6). This effect was due to significantly enhanced memory recall after the short 12-h interval in the sleep condition compared with the day wake condition ( $t_{10} = 2.9, p = .02$ ). Conditions did not differ in the 72-h and 144-h groups ( $F_{1,11} = .6, p = .45$ ; and  $F_{1,10.4} = .7, p = .40$ , respectively).



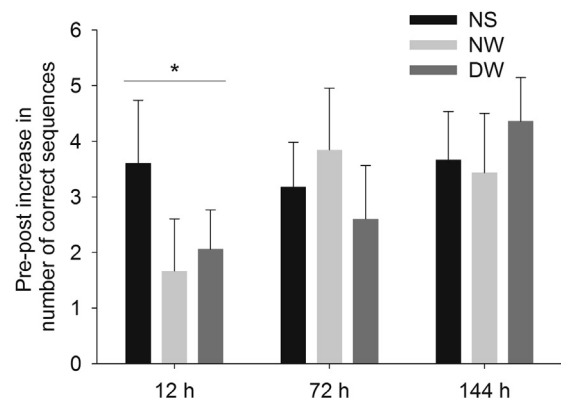
**Fig. 6 – Retention of consonant-vocal-consonant syllables. A. recall performance on the first trial. B. Reduction in number of trials needed to achieve perfect performance compared with initial learning. Similar to word pair learning, a significant positive effect of sleep can only be found on the first day after learning. Again, fatigue cannot explain differences between night sleep (NS) and wakefulness, because performance in the night wake condition (NW) does not differ from performance in the day wake condition (DW), although fatigue is much higher after a night of wakefulness.**

Similarly, a significant effect of condition was found on the number of trials required to re-learn the task (saving score) in the 12-h group ( $F_{1,10} = 6.2, p = .03$ ), which was based on higher recall scores in the sleep condition compared with both the night wake ( $t_{10} = 2.0, p = .07$ ) and day wake conditions ( $t_{10} = 2.0, p = .08$ ). Again, no differences between conditions was found in the 72-h and 144-h groups ( $F_{1,11} < .1, p = .96$ ; and  $F_{1,11} = .4, p = .56$ , respectively).

**2.2.2.2. PROCEDURAL MEMORY.** Results of the finger tapping task showed a similar pattern as the syllable recall task. Again, we find a significant effect of sleep only in the 12-h group ( $F_{2,10} = 5.7, p = .02$ ; see Fig. 7). If sleep followed learning participants show a larger increase in the number of correctly typed sequences. In the 72-h and 144-h groups performance in the sleep condition is no longer superior to performance after staying awake ( $F_{2,10} = 1.2, p = .33$ ; and  $F_{2,4.9} = .3, p = .75$ , respectively). This lack of effect can be attributed to a recovery of performance in the wake conditions, with a similarly large increase in the number of correctly typed sequences as the in the 12-h group sleep condition and both sleep conditions in the 72-h and 144-h groups, suggesting that participants catch up on the boost in performance caused by sleep following learning during the first recovery night. Initial learning performance was identical in all groups and conditions: there was no interaction between conditions (NS, NW, DW) and delay group ( $F_{4,33} = .5, p = .74$ ), and no main effect between delay groups ( $F_{2,33} = .2, p = .80$ ). However, a difference in initial performance between conditions cannot be excluded: we find an inconclusive main effect of condition ( $F_{2,33} = 2.1, p = .14$ ; see Table 1), and a borderline significant post hoc comparison between the night sleep and the day wake condition ( $t_{33} = 2.0, p = .06$ ;  $t_{33} = 1.4, p = .16$  for night wake vs day wake). Thus, we cannot exclude circadian influences on initial motor learning,

with better learning performance in the evening than in the morning.

**2.2.2.3. SLEEP.** According to their sleep logs, participants slept 7 h 51 min ( $\pm 9$  min) on average during the night after learning, which was verified by actimetry. Sleep length did not differ between the delay groups ( $F_{2,32} = .3, p = .74$ ). During the days before the experiment, participants slept on average 7 h 41 min ( $\pm 6$  min). Sleep durations before the experiment also did not differ between groups ( $F_{2,33} = .6, p = .55$ ).



**Fig. 7 – Performance in the finger tapping task shows the same pattern as the declarative memory tasks. A consolidation related increase is found after sleep on the first day, but this benefit of sleep disappears after further nights of recovery sleep. However, fatigue, which is higher after a night of wakefulness (NW) than after daytime wakefulness (DW), does not seem to explain reduced performance in the 12-h condition.**

**Table 1 – Detailed results of the finger-tapping task (S: night sleep, SD: night wake, W: day wake; mean  $\pm$  s.e.m.).**

Duration		Number of correct sequences		
		Pre	Post	Difference
12 h	S	20.3 $\pm$ 1.3	23.9 $\pm$ 2.2	3.6 $\pm$ 1.1
	SD	20.6 $\pm$ 1.5	22.3 $\pm$ 2.2	1.7 $\pm$ 0.9
	W	19.2 $\pm$ 2.1	21.2 $\pm$ 2.4	2.1 $\pm$ 0.7
72 h	S	21.5 $\pm$ 1.2	24.6 $\pm$ 1.5	3.2 $\pm$ 0.8
	SD	20.9 $\pm$ 1.4	24.7 $\pm$ 2.2	3.8 $\pm$ 1.1
	W	19.2 $\pm$ 1.7	21.8 $\pm$ 2.3	2.6 $\pm$ 1.0
144 h	S	19.1 $\pm$ 1.7	22.8 $\pm$ 1.9	3.7 $\pm$ 0.9
	SD	17.6 $\pm$ 1.5	21.0 $\pm$ 2.1	3.4 $\pm$ 1.1
	W	18.4 $\pm$ 1.7	22.7 $\pm$ 2.3	4.4 $\pm$ 0.8

### 3. Discussion

Because evidence for persistent effects of sleep on memory consolidation is scarce, we tested whether a period of sleep during retention intervals of different lengths improves memory performance at delayed testing compared with periods of wakefulness. For all tasks, we see significantly enhanced performance immediately after intervals of no more than 24 h when comparing sleep with wakefulness. Contrary to our expectations, this difference remains significant after longer retention intervals only for the mirror-tracing task. Here, a positive effect of sleep can still be seen after three additional nights of sleep. No such effect was found for the declarative memory tasks or the finger sequence tapping task. For these tasks, the performance benefit seen immediately after periods of sleep is lost after subsequent nights.

We see a persistent long-term effect of sleep on the mirror-tracing skill. Even after three recovery nights, performance is better if participants were allowed to sleep after learning mirror-tracing than if they were sleep deprived. Therefore, we can conclude that there are sleep-dependent processes that have to occur during a specific time window after learning in order for memory enhancement to occur for this task. Actually, accuracy of mirror-tracing improved little or not at all if participants did not sleep after learning. On the behavioral level, this finding is similar to that of Stickgold et al. (2000), who reported an improvement in visual discrimination skill only when participants were allowed to sleep during the first night after training. Their study is particularly remarkable because it is one of the rare studies showing a process of memory consolidation that strongly requires sleep, i.e., it shows no improvement without sleep. In the present study, mirror-tracing skills improved during training, and this improvement remained stable between test sessions. However, only if participants slept after training, additional off-line improvements were seen. This is another similarity to the findings of Stickgold et al. who found that visuo-motor skill training leads to an improvement only if it was followed by sleep. Whether the off-line improvements we observe in the mirror-tracing task depend on similar underlying mechanisms as sleep-dependent improvements of the visuo-motor skill remains open. It must be noted that visual discrimination and motor learning are skills which recruit

very different neuroanatomical substrates. However, both tasks rely at least partially on neocortical plasticity (Inoue et al., 1997; Schwartz, Maquet, & Frith, 2002) and for both, no hippocampal contribution has been shown, yet. We therefore believe that it is possible that they rely on similar sleep-related synaptic consolidation mechanisms.

Although our results do not show long-term benefits of one night of sleep for all memory tasks, they do not exclude an essential role of sleep in memory consolidation in these tasks. Even in those tasks that do not show long-term effects, restoration of performance seen after sleep following initial wakefulness can be explained by active consolidation processes as well as by relief of fatigue. Intriguingly, all tasks, which did not show long-term effects, have been assumed to rely on a strong hippocampal contribution. This is obvious for word pair learning and nonsense syllables, but even the finger tapping task has been shown to activate the hippocampus during learning (Schendan, Searl, Melrose, & Stern, 2003; Walker et al., 2005). The role of the hippocampus in finger tapping could encompass explicit aspects of sequence learning (Devito & Eichenbaum, 2011), but recent research shows that it could also be related to implicit aspects of the task, with hippocampal activation present, even when the participants were completely unaware of the sequential structure of the task (Albouy et al., 2008; Gheysen, Van Opstal, Roggeman, Van Waelvelde, & Fias, 2011; Rose, Haider, Weiller, & Büchel, 2002; Schendan et al., 2003). This common contribution of the hippocampus can explain why finger tapping shows a similar time course of consolidation as the declarative memory tasks. A major function of the hippocampus is supposed to be the short-term buffering of new information (McClelland, McNaughton, & O'Reilly, 1995; Rolls & Treves, 1994). The model of complementary learning systems assumes that the hippocampus is a fast learning system, which acquires information more quickly, but at the same time also forgets more quickly (McClelland et al., 1995). It is likely that information is buffered until systems consolidation of new memories can occur, even over a prolonged period of wakefulness. Such a buffer would certainly make sense because unique and perhaps vital new memories should not be lost when encoding is followed by a lack of sleep. Therefore, effects of sleep loss can be compensated in hippocampal-dependent tasks. Acquisition of procedural tasks without hippocampal contributions, on the other hand, is usually slow and relies on a large number of repetitions. Consolidation of this type of memory seems to benefit lastingly from sleep and suffers from prolonged periods of wakefulness after encoding.

The difference in behavior between the mirror-tracing task and the other, hippocampal-dependent tasks lends to the conclusion that there are qualitatively different sleep-related memory consolidation processes. Currently, there are no generally accepted theories that can explain how different memory tasks depend on different consolidation processes. There are, however, two models of how sleep can influence memory consolidation, one relying on processes of systems consolidation (Gais & Born, 2004), the other on mechanisms of synaptic consolidation (Tononi & Cirelli, 2003). Reactivation theory suggests that hippocampal learning activity is replayed during sleep, leading to an active strengthening of these traces and their integration into neocortical networks (Rasch & Born,



2007). External reactivation has been shown to boost memory consolidation in both declarative (Rasch et al., 2007; Rudoy, Voss, Westerberg, & Paller, 2009) and finger sequence tasks (Schönauer et al., 2014). Synaptic models of consolidation, on the other hand, assume that molecular changes induced during learning have delayed consequences, which could be mediated or modulated by sleep (Dumoulin et al., 2013). Systemic reactivation and synaptic consolidation are thought to be concurrently involved in consolidation of hippocampal-dependent memories (Mascetti et al., 2013), with trace reactivation early during sleep preparing cortical synapses for later occurring plasticity processes (Diekelmann & Born, 2010). Non-hippocampal procedural tasks like mirror-tracing, on the other hand, have not been shown to rely in a similar way on reactivation and systems interaction between different memory networks. It is tempting to speculate that hippocampal buffering and trace reactivation during sleep mediates the recovery of memory performance after the first night of sleep in the declarative memory tasks and the finger sequence tapping task. In contrast, in tasks without hippocampal involvement, synaptic consolidation may need to occur within a defined time window after encoding in order to be effective. While it is very speculative which mechanism underlies which sleep-related effect, findings clearly speak for the existence of at least two distinguishable, sleep-related mechanisms, which affect memory consolidation (Geyer et al., 2013).

Our findings obviously raise the question whether the effects of sleep on memory, which have been reported in numerous studies during the last decade, can be explained fully by consolidation processes, i.e., by additional strengthening of memory traces during night sleep, or whether general or specific fatigue, caused by prolonged wakefulness and task-related strain, respectively, contribute to observed effects. Although present experiments cannot resolve this question, we have reason to believe that the missing long-term effects are due to delayed action of sleep on hippocampally-buffered memory. In general, there is very little evidence that fatigue, as induced by less than 40 h of sleep deprivation, can actually impair declarative memory recall (Quigley, Green, Morgan, Idzikowski, & King, 2000). In the first experiment, no significant impairment of word pair recall by sleep deprivation before recall was found, and also recall of names from long-term memory was not impaired by sleep deprivation. Furthermore, in the second experiment, no difference was found between daytime and nighttime wakefulness, although nighttime wakefulness (i.e., sleep deprivation) is much more fatiguing. Actually, the night wake group numerically even performed slightly better than the day wake group on syllable recall, which might result from an additional circadian influence on memory performance. Similarly, in another study, the length of a prior wake period did not influence recall performance (Gais et al., 2006). Fatigue has been discussed extensively as a cause for apparent sleep-related improvements with regard to procedural memory (Keisler, Ashe, & Willingham, 2007; Sheth, Janvelyan, & Khan, 2008; Song, Howard, & Howard, 2007). However, for procedural mirror-tracing performance, our data show a definite, long-lasting improvement, which must be independent of fatigue. Therefore, we conclude that for

procedural memory, active, sleep-dependent consolidation processes exist. These may interact with influences of fatigue. For hippocampally-buffered memory, we assume that delaying the sleep period mainly postpones sleep-related consolidation processes, because there is little indication that fatigue induced by temporary sleep loss significantly impairs recall performance.

In our data, we find that sleep-related improvement is only seen for semantically related word pairs, but not for unrelated pairs. This observation is in line with the findings of Plihal and Born (1997) who also use related word pairs, but does not support the findings of Payne et al. (2012), who report effects exclusively in semantically unrelated material. In view of the literature, which shows sleep effects with both types of material, we assume that semantically related and unrelated word pairs alike benefit from sleep. Whether an effect of sleep becomes apparent may be modulated by strength of initial encoding, which depends on the learning skill of the participants and difficulty of the material. Encoding strength in turn can modulate consolidation during sleep either positively or negatively (Drosopoulos, Schulze, Fischer, & Born, 2007; Tucker & Fishbein, 2008). Whether complex interactions of stimulus material and experimental design, or a mere lack of statistical power is responsible for divergent findings, remains open.

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#### 4. Conclusions

In conclusion, our data confirm that sleep has an enduring influence on memory performance. We find evidence for two distinct sleep-related memory consolidation processes, which differ with regard to their development over time. On the one hand, we observe short-term enhancement of performance after the first interval of sleep or wakefulness in both declarative and procedural memory tests that have previously been associated with hippocampal activity during learning. These effects are only temporary and disappear after recovery sleep. Because there is little evidence that memory retrieval is impaired by fatigue in our and previous studies, and because fMRI studies have shown long lasting consolidation-related changes in brain activity without overt changes in performance (Orban et al., 2006), we believe that the lack of enduring behavioral effect is rather due to temporary memory buffering and delayed consolidation than to fatigue after wakefulness. On the other hand, for a hippocampal-independent motor learning task, sleep provides long-lasting benefits, which remain stable even after several recovery nights. We suggest that these two consolidation processes are based on two different mechanisms. Whereas the actual mechanisms are not known, it can be speculated that more complex forms of consolidation rely on memory trace reactivation and systems interactions whereas purely implicit motor memory only requires strengthening of synaptic connections, which has to occur shortly after learning.

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