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Sleep-learning Impairs Subsequent Wake-learning

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Abstract

Humans can unconsciously acquire new information during deep sleep. Although sleep-played information can guide behavior during subsequent wakefulness, sleep-formed memories cannot be remembered consciously after awakening. We explored whether sleep-learning might expedite conscious learning during subsequent wakefulness by providing a first bout of carving a new memory trace, which ensuing wake-learning can build on. We analyzed previously unreported data acquired in a recent study on vocabulary learning during slow-wave sleep (Züst et al., 2019, Curr Biol). Sleep-played vocabulary was successfully retrieved in an implicit memory test administered following awakening. However, sleep-learning diminished instead of increased wake relearning of the same vocabulary. We speculate that vocabulary learning during sleep may have interfered with the synaptic down-scaling of hippocampal and neocortical language-related neurons, which were then too saturated for further potentiation required for the wake-relearning of the same vocabulary.

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Introduction

Growing evidence suggests that humans can unconsciously process and store new information during deep sleep and that this information transfers into wakefulness (Andrillon et al., 2017; Arzi et al., 2014, 2012; Ruch et al., 2014; Ruch and Henke, 2020; Züst et al., 2019). However, sleep-formed memories cannot be remembered consciously after awakening because memories were formed in the unconscious state of deep (slow-wave) sleep. Sleep-formed memories merely exert implicit, indirect effects on awake behavior (Ruch and Henke, 2020), which may limit the usefulness of sleep-learning. Here, we explored whether sleep-learning might expedite conscious, willful relearning of the same content during subsequent wakefulness. A first bout of carving a new memory trace during sleep might build a fundament on which ensuing wake-learning can build on. We analyzed previously unreported data acquired in a recent study on vocabulary learning during slow-wave sleep (SWS) (Züst et al., 2019). In our previous report, we observed that new vocabulary was encoded and retained during SWS when vocabulary presentation coincided with peaks of slow-waves. Successful retrieval of sleep-formed vocabulary in an implicit memory test administered after waking recruited hippocampus and language areas (Züst et al., 2019). We concluded that vocabulary learning during sleep was mediated by the wake-like neuronal activity provided by slow-wave peaks (Andrillon and Kouider, 2020; Destexhe et al., 2007) and recruited the same hippocampal-neocortical network that is involved in vocabulary learning during wakefulness (Breitenstein et al., 2005). Here, we present additional data from a subset of participants of our previous study in whom we investigated how sleep-formed memories interact with wake-learning. Participants included in this report were subjected to the same experiment as reported in the previous study: they listened to new vocabulary during SWS and took an implicit memory test following waking. In addition, these participants then also tried to consciously relearn the sleep-played vocabulary as well as new vocabulary.

Results & Discussion

We played fake foreign words combined with translation words (e.g., *guga*-ship) to 26 participants in slow-wave sleep (SWS) during an afternoon nap (Fig. 1A). Each word pair was repeated

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four times in sequence. Translation words designated either large (e.g., ship) or small (e.g., brush) objects. Following awakening, participants took an implicit memory test which assessed whether sleep-learning was successful. We represented the previously sleep-played foreign words during this test for participants to guess whether a foreign word designated a large or small object. Participants' guessing accuracy exceeded chance (50%) level (accuracy: 60.5%, $X^2(1) = 11.302$, $p < .001$), when the second word of a pair had coincided with a slow-wave peak in at least two of the four presentations of a word pair (0-1 peaks: accuracy = 49.8%, $X^2(1) = 0.013$, $p = .907$; 2-4 vs. 0-1 peaks: Likelihoo Ratio LR(df = 1) = 8.783, p = .003; Fig. 1B) (Züst et al., 2019). Hence, new semantic word-word associations could be stored for the long-term during SWS peaks, a time when neural excitability is increased and neuronal network properties resemble those of the waking state (Andrillon and Kouider, 2020; Destexhe et al., 2007).

Next, we explored whether the wake relearning of the same as opposed to different semantic word-word associations would profit from sleep-learning, if sleep-learning had happened during slow-wave peaks. In the congruent condition, we combined half of the sleep-played foreign words with synonyms of their sleep-played translation words (wake: *guga*-boat, sleep: *guga*-ship) because we were interested in semantic (hippocampal) rather than perceptual (neocortical) associative learning. In the incongruent condition, we recombined sleep-played foreign words and synonyms of sleep-played translation words for participants to learn new translations to previously sleep-played foreign words. If a foreign word was combined with a small object during sleep (*biktum*-brush), it was recombined with a large object at wake (*biktum*-castle), and vice versa. In the baseline condition, we presented new foreign words and new translation words to track the normal speed of learning when learning was uninfluenced by previous sleep-learning (Fig. 1C). An initial learning run was followed by four recall-and-relearning runs, during which participants first tried to recall the translation word in response to a foreign word and then received feedback (the correct translation). This allowed establishing learning curves over four runs in three conditions. Over all conditions, participants' recall performance increased from run to run (LR(1) = 709.793, p<.001). Recall performance was not modulated by condition alone (congruent/incongruent/baseline; LR(2) = 1.130, p = . 568). Condition influenced recall performance only

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in interaction with the number of peak-associated stimulations during sleep (0-1 vs. 2-4 peaks) – i.e., whether sleep-learning had happened during SWS peaks or not (LR(1) = 4.231, p = .040). Wake learning in the congruent condition was paradoxically diminished (rather than enhanced) when previous sleep-learning had occurred during two or more SWS peaks (0-1 vs. 2-4 peaks: LR(1) = 5.126, p = .024), while wake learning in the incongruent condition was not modulated by number of SWS peaks during sleep-learning (LR(1) = 0.923, p = .337). Importantly, recall performance in the congruent condition was lower across all 4 runs compared to baseline when sleep-learning had occurred during two or more SWS peaks (LR(1) = 4.185, p = 0.041; Fig. 1D); retrieval performance dropped more than 8% in the last run (36.2% vs. 44.7% recalled associations). Neither recall performance in the incongruent condition nor the recall of congruent pairs, which had been learned during only 1 or no SWS peaks, differed from baseline (all p > .233).

Andrillon et al. (2017) reported a similarly paradoxical finding using a non-hippocampal perceptual learning task given during deep slow-wave sleep and again at wake. Their participants' wake ability to learn to detect repeating noise patterns in a stream of random noise was impaired if the same noise patterns had been presented during SWS but not if the patterns were new or had been presented during REM sleep or light non-REM sleep (Andrillon et al., 2017). What mechanism might cause the impairment of wake-learning following sleep-learning? SWS is crucial for synaptic homeostasis, which prepares the brain for efficient wake-learning. Unused and irrelevant synapses are down-scaled to compensate for the synaptic potentiation during wakefulness (Tononi and Cirelli, 2014), which renews the brain's learning capability and facilitates memory retrieval (Tononi and Cirelli, 2014). According to Andrillon et al. (2017), stimulus presentation during SWS might lead to a stronger synaptic down-scaling in neurons that are activated by the stimuli. However, a strong synaptic down-scaling in stimulus-specific networks cannot account for our participants' successful implicit retrieval of sleep-learned associations. At the contrary, new semantic associations had apparently been formed during peaks of slow-waves when neurons were excitable (Andrillon and Kouider, 2020; Destexhe et al., 2007) and when synaptic potentiation was possible. Therefore, we believe that semantic associative learning of the sleep-played

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vocabulary had interfered with the synaptic down-scaling within hippocampal and neocortical language-related neurons engaged in the learning of specific semantic associations. There is evidence that neurons can be spared from down-scaling if they are highly active during sleep (Gulati et al., 2017; Tononi and Cirelli, 2020). Because synaptic renormalization was inhibited by sleep-learning, the involved neurons were saturated following awakening and therefore lacked the capacity for further potentiation required for conscious vocabulary learning. Interestingly, the wake-learning of new semantic associations in the incongruent condition was not diminished. Hence, the deficient synaptic renormalization was specific to those neurons that generated the sleep- and ensuing wake-learning of the same semantic associations.

Here, we speculate that sleep-learning impairs subsequent wakeful relearning of the same content by selectively interfering with synaptic renormalization in those neurons that encode the sleep-played information. If this account is correct, then an additional episode of recovery sleep between sleep-learning and awake relearning could mitigate or even nullify the negative impact of sleep-learning on relearning. Recovery sleep would reestablish synaptic homeostasis in those neurons that were activated during learning in the previous nap and would renew these neurons' learning capacity (Mander et al., 2011). This in turn could allow sleep-formed memories to facilitate subsequent wake relearning of the same information.

We conclude that the brain can acquire new relational information during deep sleep. However, sleep-acquired information appears to defy conscious access. Furthermore, sleep-formed memories tend to impair rather than improve conscious, willful relearning of the same content during subsequent wakefulness. This severely limits practical applications of sleep-learning.

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Figures legends

Figure 1. Design and Results. A) Pairs of fake foreign words and translations words were presented at a steady rhythm (word onset interval: 1.075 ms, pair onset interval: 4.3 s) during slow-wave sleep. We counted the number of times the second word of each pair coincided with a slow-wave peak (blue) across the four repetitions of the pair. B) Implicit memory test applied following waking to assess unconscious retrieval of sleep-played vocabulary. Implicit memory was measured as % correct guesses. Guessing accuracy exceeded chance level (50%) for items, where the 2nd word of a pair was played into a slow-wave peak more than once. C) Conscious relearning of the sleep-played foreign words paired with congruent translations (=) and with incongruent (≠) translations. New foreign words and new translation words (★) served as baseline. D) Recall performance in the four conscious recall-and-relearning runs per condition (congruent and incongruent condition: blue line; baseline: ocher line). The recall of congruent translations was impaired if sleep-learning was successful, i.e., when vocabulary presentation during sleep had coincided with a slow-wave peak more than once (comparison to baseline in rightmost panel; comparison within congruent condition: two rightmost panels); Plots display % correct guesses (B) or % recalled (D). Error bars indicate binomial standard errors. *p <.05, **p<.01,***p<.001.

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Materials and Methods

Participants

We report the data of a subgroup of participants (N = 26, age 19-32, mean ± SD = 22.96 ± 3.41; 18 (69%) female) from a recently published study on vocabulary learning during slow-wave sleep (SWS)(Züst et al., 2019). The participants included in the current report were subjected to the same experiment as reported in the original study: they listened to new vocabulary during SWS and took an implicit memory test following waking. However, participants then also tried to consciously relearn the sleep-played vocabulary. For detailed information about participants, stimuli, stimulation during sleep, the implicit memory test, and data acquisition see the original article. The study protocol was approved by the local ethics committee “Kantonale Ethikkommission Bern”.

Sample size was estimated based on previous studies on verbal learning during sleep (Andrillon and Kouider, 2016, N = 22; Cox et al., 2014, N = 12; Ruch et al., 2014, N = 16) and using a power analysis with an expected effect size of 5%, a standard deviation of 10%, and an intended statistical power of 0.8 (one-tailed testing). This analysis was performed with G*power (Faul et al., 2007) and suggested an optimal sample size of 26 participants.

General procedure

Participants arrived at the sleep laboratory at noon, after a night of partial sleep restriction. They gave written informed consent, were outfitted with EEG electrodes and with in-ear headphones, took a hearing test, and then went to sleep for an afternoon nap. Throughout the entire nap, Brownian noise was quietly presented via headphones to reduce the salience of vocabulary presentation. Once the EEG showed clearly visible slow-wave activity (SWS or N2 sleep at the transition to SWS), we started the presentation of pairs of foreign words and translation words for vocabulary learning during sleep. Half of the sleep-played translation words designated large objects (e.g. ship), and half small objects (e.g. brush). Each word pair was repeated four times in sequence with swapped positions (*guga*-ship, ship-*guga*, *guga*-ship, ship-*guga*) to induce a flexible representation of the semantic word-word associations. Words were

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presented at a steady rhythm (onset interval between single-words of a pair: 1.075 ms; onset interval between pairs: 4.3 s) that mimicked the frequency of endogenous slow-waves(Ngo et al., 2013).

Once all word pairs were played, participants were wakened and were given some time to recover from sleep inertia. Then, participants took an implicit memory test. This test required participants to guess whether previously sleep-played foreign words and new foreign words designated large or small objects. Responses were correct if they matched the category (large/small) of the sleep-played translation words. Responses to new foreign words were not classified as correct or incorrect but were used to identify foreign words that were disproportionally rated as large or small (see stimulus inclusion and exclusion).

Participants were then asked to consciously relearn the sleep-played vocabulary. Half of the sleep-played foreign words were paired with synonyms of their sleep-played translations (congruent condition). The remaining foreign words were randomly paired with synonyms of sleep-played translations that had been combined with other foreign words (incongruent condition). If a foreign word was combined with a small object during sleep, it was combined with a large object at wake, and vice versa in the incongruent condition (Fig. 1C). Synonyms instead of the actual sleep-played translation words were used to test whether sleep-learning yielded semantic (hippocampus-dependent) rather than mere perceptual (neocortical) word-word associations. Relearning was expected to be expedited due to semantic congruence in the congruent condition and impaired due to semantic interference in the incongruent condition. New foreign words that had not been played during sleep were combined with new translation words in the baseline condition of conscious relearning. During an initial relearning run, all pairs of foreign words and translation words were presented in random order. The pairs were presented simultaneously visually on screen and acoustically via loudspeakers. Each pair was displayed for 5 s on screen (e.g. “guga = boat”). With onset of the visual presentation, first the foreign word and then the translation word (onset interval = 1 s) were sounded over loudspeakers. The initial relearning run was followed by four runs of a recall-and-relearning task. Here, participants were asked to produce the consciously learned translation word. Then, the correct translation word was provided (even if the

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response was correct). The order of word pairs was re-randomized on each run. On each trial, participants were first presented with a blank black screen (500 ms) followed by a fixation screen with a central white dot, which was then followed by the visual and acoustic presentation of a foreign word (e.g. “guga = “). Participants were asked to read and listen to the foreign word and to then verbally report the translation word, when a question mark appeared next to the foreign word (“guga = ?“; onset delay: 1.5 s). Verbal responses were recorded using a voice recorder (Olympus WS-700M) and were saved for later analysis. The experimenter proceeded to the feedback trial as soon as a participant provided an answer, or after 5s if no answer was provided. In the feedback trial, the correct translation word was displayed on screen (“guga = boat”) for 2 s and was played simultaneously via loudspeaker. Participants took a short break when half of the word-pairs in a run had been processed and again at the end of a run. The conscious relearning task lasted about 45 minutes.

Stimulus material

We used legal, pronounceable, two-syllabic pseudowords (e.g. *guga*) as words of a fake foreign language to study vocabulary acquisition during sleep. Foreign words were created by assembling Dutch and German syllables. We compiled three lists of 24 foreign words each. Each list also contained 24 German synonym pairs to be used as translation words for sleep-learning and wake-learning (e.g. ship-boat). Half of the synonym-pairs in each list stood for large objects (ship-boat), and half for small objects (revolver-pistol) with respect to the size of a shoebox. Lists were matched for mean word length, pronounceability, perceived concreteness (foreign words), and lexical frequency (translation words). For each participant, one of each list was randomly assigned to one of the relearning conditions (congruent, incongruent, baseline). Lists were thus counterbalanced across conditions and participants. Within each list, pairs of foreign words and translation words were generated randomly for each participant. The translation words selected for presentation during sleep (e.g. “ship” of the synonym pair “ship-boat”) were never used as synonyms during conscious re-learning in the waking state and vice-versa. An additional list of 24 foreign words was never played during sleep but was only used in the implicit memory test.

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Stimulus inclusion and exclusion

Word-pairs that were selected for presentation during sleep were excluded from analysis if they were not presented during sleep due to a participant's insufficient sleep duration, if they were presented outside of slow-wave rich N2 sleep or slow-wave sleep, or if they were played during an arousal period. We further identified and excluded from all data analyses the two most consistently small-rated and the two most consistently large-rated foreign words in each word lists based on participants' ratings of these words in the baseline condition in the implicit memory test (for details see original study(Züst et al., 2019)). These foreign words were inherently associated with a specific meaning, e.g. due to their phonetic similarity to existing words. They were excluded from analyses because they were expected to yield poor learning. The average number of word pairs available for analysis per participant was 17.9 (SD = 2.1) in the congruent condition and 17.8 (SD = 2.6) in the incongruent and 19.3 (SD = 0.5) in the baseline condition.

Electroencephalography

Our recent study revealed that vocabulary learning during SWS was possible if the second word of a pair was repeatedly played during an ongoing slow-wave peak(Züst et al., 2019). This means that sleep-learning was successful if slow-waves peaked between -275 and 25 ms around the onset of the presentation of the second word of a pair more than once within four repetitions. To determine whether the second word of a pair coincided with a peak, we first referenced the raw EEG signal (64 channels, 10-20 montage, 500 Hz sampling rate) to the global average and then extracted the average signal over frontal electrodes (F1, F2, Fz, FC1, FC2, FCz). We low-pass filtered the resulting signal at 4 Hz and then performed a time-frequency decomposition (Morlet wavelet transformations with two cycles in length) to extract the instantaneous phase of 0.8 Hz oscillations at 20 intervals. The second word of a pair was said to coincide with a slow-wave peak if the phase of 0.8 Hz oscillations was within ± 2.5% (i.e. ± 9°) around the peak phase (i.e. 0°) in the interval from 275 ms before to 25 ms after the onset of the second word. We

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determined the number of word pairs that were played during a slow-wave peak twice or more often versus never or only once.

Significance testing

To find out whether the number of peak-associated stimulations (0-1 vs. 2-4 peaks) or the relearning condition (congruent/incongruent/baseline) modulated retrieval performance on the implicit memory test or recall performance on the conscious relearning task, we performed mixed effects logistic regressions at the single trial level. The dependent variables were guessing accuracy on the implicit memory test (correct vs. incorrect) and conscious recall on the recall-and-relearning task (correct vs. incorrect). Analyses were performed using cumulative link mixed models (CLMMs) with Laplacian approximation as implemented in the function “clmm” provided by the package “ordinal” (v2019.4-25)(Christensen, 2019) for the software R (v 3.6.1)(R Core Team, 2019). We modeled random intercepts for participants and for foreign words. We stepwise entered factors of interests into the random intercept models and performed likelihood ratio tests to assess whether adding the entered factor improved the model fit. Likelihod ratios (LR(df)) with the respective degrees of freedom (df) and the corresponding p-values are reported.

For performance on the implicit memory test (N trials = 927), we first analyzed the effect of relearning condition (congruent vs. incongruent), then the effect of the number of peak-associated stimulations (0-1 vs. 2-4 peaks), and then the effect of the interaction between condition and number of peak associated stimulations. As expected, guessing accuracy was not significantly different between foreign words that were later consciously relearned with congruent vs. incongruent translations (effect of condition: LR(1) = 0.485 , p = .486), even if tested in interaction with the number of peak-associated stimulations (LR(1) = 0.441, p = .506). Hence, there was no evidence for an a-priori difference in sleep-learning between word pairs that were later consciously relearned with congruent versus incongruent translations. Only the number of peak-associated stimulations (0-1 vs. 2-4 peaks) reached significance (see

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main text; LR(1) = 8.783, p = .003). We tested whether performance deviated from chance level (50%) in each condition (0-1 vs. 2-4 peaks) using X^2 tests (see main text).

For performance on the conscious recall test (N trials = 5712), we first analyzed the effect of test run (recall-and relearning run 1-4), then condition (congruent/incongruent/baseline), and then the interaction between condition and test run. Performance significantly improved with each test run (LR(1) = 709.793, p < .001) but was not significantly modulated by condition (LR(2) = 1.130, p = .568) or the interaction between condition and run (LR(2) = 3.536, p = .171). Hence, neither the average performance across test runs, nor the increase in performance across runs was modulated by condition alone.

To assess whether the effect of condition (congruent/incongruent) depended on the number of peak-associated stimulations during sleep, we excluded the baseline trials from analysis. We then analyzed the effect of test run, condition, the number of peak-associated stimulations (0-1 vs. 2-4), and the interaction between condition and peak-associated stimulations. Performance increased with each run (LR(1) = 430.984, p < .001) but was not modulated by condition (congruent/incongruent: LR(1) = 0.693, p = .405). The number of peak-associated stimulations alone did not influence performance (0-1 vs 2-4 peaks: LR(1)= 2.438, p = .118) but significantly interacted with condition (LR(1) = 4.231, p = .040). Separate analyses of word pairs in the congruent and incongruent conditions (significant effect of run in both analyses: p < .001) revealed a significant effect of the number of peak-associated stimulations (2-4 vs. 0-1 peaks) in the congruent (LR(1) = 5.126, p = .024) but not the incongruent condition (LR(1) = 0.923, p = .337). Finally, we separately compared the conscious recall of congruent and incongruent pairs that were never or once vs. repeatedly associated with slow-wave peaks with the conscious recall in the baseline condition (sig. effect of run in all four analyses: p < .001). Condition (sleep-played vs. baseline) significantly influenced recall performance for congruent pairs that had been repeatedly played during slow-wave peaks (LR(1) = 4.185, p = 0.041; all other analyses: p > .233).

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The Fig. 1 displays % correct guesses and % correctly recalled translations within each condition. Error bars indicate one binomial standard error for the reported probabilities (p) as computed with the formula: sqrt(p*(1-p)/n); where p = the reported probability, n = the number of trials.

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Author contributions

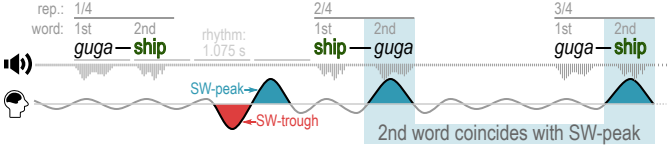
Conceptualization, M.A.Z., S.R., and K.H.; Methodology, S.R., M.A.Z., and K.H.; Investigation, M.A.Z. and S.R.; Formal Analysis, SR; Resources, S.R., M.A.Z., and K.H.; Writing – Original Draft, S.R.; Writing – Review & Editing, S.R., M.A.Z., and K.H.; Visualization, S.R.; Supervision, K.H.; Project Administration, K.H.; Funding Acquisition, K.H., and M.A.Z.

Declaration of interests

The authors declare no competing interests.

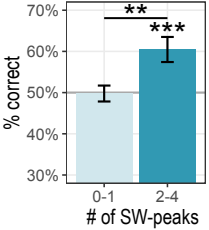
Figures

A. Vocabulary Presentation During Sleep



B. Implicit Memory

Task: *"guga: **large**/small?"*



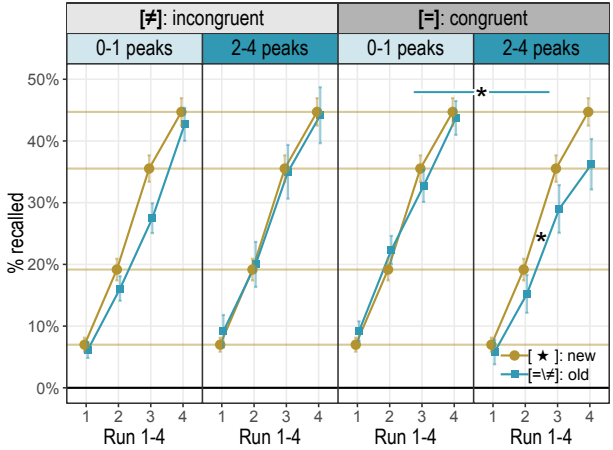
C. Wakeful Relearning Conditions

Sleep-played → Wake-learned } **Condition:**

guga-**ship** → *guga*-**boat**
tofer-**revolver** → *tofer*-**pistol**
} **[=]** (congruent)

aryl-**fortress** → *aryl*-**comb**
biktum-**brush** → *biktum*-**castle**
} **[≠]** (incongruent)

resun-**table**
lundel-**diamond**
} **[★]** (new/baseline)

D. Conscious Recall And Relearning

Recall test (4x): *"guga = ... ?"* ➡ **Relearning:** *"guga = boat"*