Vocabulary learning benefits from REM after slow-wave sleep

Laura J. Batterink [a,*], Carmen E. Westerberg [b], Ken A. Paller [a]

[a] Northwestern University, United States
[b] Texas State University, United States

ABSTRACT

Memory reactivation during slow-wave sleep (SWS) influences the consolidation of recently acquired knowledge. This reactivation occurs spontaneously during sleep but can also be triggered by presenting learning-related cues, a technique known as targeted memory reactivation (TMR). Here we examined whether TMR can improve vocabulary learning. Participants learned the meanings of 60 novel words. Auditory cues for half the words were subsequently presented during SWS in an afternoon nap. Memory performance for cued versus uncued words did not differ at the group level but was systematically influenced by REM sleep duration. Participants who obtained relatively greater amounts of REM showed a significant benefit for cued relative to uncued words, whereas participants who obtained little or no REM demonstrated a significant effect in the opposite direction. We propose that REM after SWS may be critical for the consolidation of highly integrative memories, such as new vocabulary. Reactivation during SWS may allow newly encoded memories to be associated with other information, but this association can include disruptive linkages with pre-existing memories. Subsequent REM sleep may then be particularly beneficial for integrating new memories into appropriate pre-existing memory networks. These findings support the general proposition that memory storage benefits optimally from a cyclic succession of SWS and REM.

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1. Introduction

Optimal learning requires a balance between rapidly acquiring new information and retaining older but still useful memories, a conflict known as the "stability-plasticity dilemma" (e.g., Carpenter & Grossberg, 1988; Abraham & Robins, 2005). Two-stage models of memory consolidation offer a solution to this issue (Marr, 1971; Alvarez & Squire, 1994; McClelland, McNaughton, & O'Reilly, 1995; Frankland & Bontempi, 2005). These models propose that new information is initially encoded in parallel into both a fast-learning temporary store, namely the hippocampus, as well as a slower-learning, long-term store, namely the neocortex. Over time, newly encoded memory representations are gradually integrated into slower-learning cortical networks such that representations can become relatively more dependent upon the cortex and less dependent upon the hippocampus. This consolidation process occurs through the spontaneous and repeated reactivation of newly encoded memory traces (Sutherland & McNaughton, 2000; cf. O'Neill, Pleydell-Bouverie, Dupret, & Csicsvari, 2010). Memory reactivation can occur during any offline period, but appears to

be especially prominent during slow-wave sleep (SWS; Wilson & McNaughton, 1994; Lee & Wilson, 2002; Ji & Wilson, 2007).

In humans and most other diurnal mammals, SWS and REM sleep alternate cyclically over the course of the night, with extended SWS periods occurring predominantly in the early part of the night and REM sleep preferentially later on (Rasch & Born, 2013). Thus periods of SWS are naturally followed by periods of rapid-eye-movement (REM) sleep. A number of theoretical models have suggested that SWS and REM play complementary roles in memory consolidation, and that memory benefits optimally from a cyclic succession of these two stages (e.g., Diekelmann & Born, 2010; Giuditta et al., 1995; Ambrosini & Giuditta, 2001; Walker & Stickgold, 2010). For example, according to the sequential hypothesis (Giuditta et al., 1995; Ambrosini & Giuditta, 2001), during SWS non-adaptive memory traces are weakened or eliminated, resulting in a relative strengthening of the remaining traces. Then, during subsequent REM sleep, these remaining traces are strengthened, integrated and stored in pre-existing knowledge networks. Another proposal is that systems consolidation occurs during SWS whereas synaptic consolidation occurs during REM sleep (Diekelmann & Born, 2010). Active systems consolidation during SWS—involving the repeated activation of newly encoded memories—drives the integration of new memories into the network of

* Corresponding author at: Northwestern University, Department of Psychology, 2029 Sheridan Road, Evanston, IL 60208, United States.
  E-mail address: lbatterink@northwestern.edu (L.J. Batterink).

pre-existing long-term memories. Subsequent REM sleep, which represents a brain state of "disengagement" or disconnection between memory systems, then acts to stabilize the transformed memories by enabling undisturbed synaptic consolidation. A third view is that SWS functions to consolidate new episodic item memories while keeping individual memory representations separate and distinct; REM then facilitates integration of these new memories with older memories, forming rich associative networks (Walker & Stickgold, 2010).

The general view that memory consolidation occurs optimally through cycles of SWS and REM sleep is supported by studies in rats that show high positive correlations between the number of SWS periods followed by REM sleep and number of avoidances on an active avoidance task (Langella et al., 1992; Ambrosini, Langella, Gironi Carnevale, & Giuditta, 1992; Ambrosini, Mariucci, Bruschelli, Colarieti, & Giuditta, 1995; Ambrosini, Sadile, Gironi Carnevale, Mattiaccio, & Giuditta, 1988; Ambrosini et al., 1993). Interestingly, the number of SWS periods followed by waking correlated negatively with number of avoidances, suggesting that memories may weaken during SWS if not followed by REM sleep (Langella et al., 1992). A more recent study found that circadian-desynchronized rats, which exhibit fragmentation of REM and NREM sleep within nonfragmented sleep bouts, demonstrated impaired long-term memory on a fear-conditioning task. Further, this impairment in memory consolidation correlated with post-training fragmentation of NREM and REM sleep (Lee et al., in press). Converging evidence has been found in humans. Performance on a verbal recall task was impaired when participants' sleep cycles were experimentally fragmented (by waking the subject 40 min after each NREM onset, disrupting the NREM-REM sequence), but not when sleep was disrupted without fragmenting NREM-REM cycles (by waking the subject 10 min after each REM onset); duration of REM sleep did not differ between the two conditions (Ficca, Lombardo, Rossi, & Salzarulo, 2000). Similarly, in elderly participants, the proportion of sleep time organized into sleep cycles predicted overnight word recall, whereas duration of any given sleep stage did not (Mazzoni et al., 1999). These results suggest that the cyclic succession of SWS and REM plays a more critical role in memory consolidation than duration of individual sleep stages per se. In addition to verbal recall, SWS and REM have been shown to make complementary or interactive contributions to many other types of memory in humans, including visual discrimination (Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000; Mednick, Nakayama, & Stickgold, 2003), emotional memory (Cairney et al., 2015), and linguistic rule generalization (Batterink, Oudiette, Reber, & Paller, 2014).

During SWS, memory reactivation occurs spontaneously, but can also be triggered externally by presenting memory cues associated with a prior learning episode, a technique known as targeted memory reactivation (TMR). TMR has been shown to enhance consolidation of declarative and nondeclarative memories (Oudiette & Paller, 2013). For example, card-pair locations learned in the presence of an odor were recalled more accurately when participants were re-exposed to the odor during SWS compared to control conditions (Rasch, Buchel, Gais, & Born, 2007). Odor presentation during SWS also elicited hippocampal activation, providing neural evidence of memory reactivation. Individual memories can also be reactivated through TMR. Rudoy et al. (2009) trained participants on the spatial locations of individual objects paired with characteristic sounds (e.g., cat–meow), and then presented half of the sounds during SWS. Participants showed better post-nap performance for objects whose associated sound had been presented during SWS compared to uncued objects. These results and others (e.g., Diekelmann, Biggel, Rasch, & Born, 2012; Diekelmann, Buchel, Born, & Rasch, 2011; Antony, Gobel, O'Hare, Reber, & Paller, 2012; Schönauer et al., 2014; Hu et al., 2015) suggest that reactivation

during SWS leads to immediate strengthening of associated memory representations.

An alternative (though not necessarily mutually exclusive) theoretical possibility is that reactivation during SWS may transiently destabilize memories (cf. Rasch & Born, 2013, 2007), providing an opportunity for integration with pre-existing memories. Rasch and Born (2007) proposed transient labilization by memory reactivation during SWS as a candidate mechanism that would allow newly acquired memories to be gradually modified through association with older long-term memories, ultimately facilitating their integration into existing networks. Subsequent consolidation processes, possibly involving REM sleep, would then strengthen the new memory. Conceivably, memory reactivation during SWS could be similar to memory reactivation that occurs during wake, which has been described as temporarily transforming the memory into an unstable state that requires "reconsolidation" (Lee, 2009; Nader & Hardt, 2009; Sara, 2000). On the other hand, the process may simply involve stages of consolidation that never reach a final, permanent state (Dudai, 2012), such that instability could naturally follow from new associative linkages and/or forgetting. Just as reactivation during wake provides the opportunity to modify and update existing memory traces with reference to newly encountered information, a similar process during sleep could allow for memory updating with reference to pre-existing knowledge, especially given the absence of external input. As this process transpires, reactivation during SWS may include transient instability, followed by a subsequent strengthening stage (Rasch & Born, 2013, 2007). We propose an alternative variation on this idea, which is that reactivation could destabilize and strengthen memories simultaneously (rather than sequentially), with some memories undergoing de-stabilization to a greater extent while others are preferentially strengthened.

The possibility that reactivation during SWS could entail transient memory instability would also be consistent with sequential views of SWS and REM in memory consolidation (e.g., Diekelmann & Born, 2010; Giuditta et al., 1995; Ambrosini & Giuditta, 2001; Walker & Stickgold, 2010). A common theme of these models is that memories must undergo further consolidation processing after SWS, with subsequent REM sleep required to stabilize and integrate the memory into pre-existing networks. In the context of TMR, learning-related cues presented during SWS may temporarily destabilize the associated memory, while subsequent REM sleep may then act to strengthen and integrate the memory into existing memory networks. Thus, effects of TMR on memory performance could conceivably interact with sleep organization.

A recent study provides support for this idea (Tamminen, Lambon Ralph, & Lewis, 2017). In this study, learners were presented with fictitious novel spoken words (e.g., cathedruke) that were each based on a familiar existing word (e.g., cathedral) while performing a phoneme-monitoring task. After this training period, lexical competition—a measure of the degree to which the novel words have been integrated into the mental lexicon—was assessed through a lexical decision task. Participants then took an afternoon nap, during which half of the novel words were cued during periods of SWS. Upon awakening, participants completed a second lexical decision task to assess potential changes in lexical competition. Although TMR did not have an overall impact on lexical competition effects, the percentage of time in REM significantly predicted the change in lexical competition for cued words, with greater duration of REM sleep associated with larger increases in lexical competition. This correlation was not observed for uncued words. Based on these results, the authors proposed that reactivation during SWS through TMR may "tag" these memories for later processing, with subsequent REM sleep then mediating their integration into lexical networks.

The current study provides additional converging evidence that duration of REM sleep following SWS influences TMR-related memory benefits, consistent with models suggesting complementary roles for SWS and REM sleep in memory consolidation. We designed our study to investigate whether TMR can improve foreign vocabulary learning, building upon a previous study that examined this same question (Schreiner, Lehmann, & Rasch, 2015). In this prior study, German-speaking participants were trained on new Dutch words and their German translations, and were then presented with half of the newly learned Dutch words during periods of SWS occurring over the first half of the night. Following cueing, participants showed improved memory recall for the German translation of the cued words relative to the uncued words. A follow-up study replicated this result, again showing that cueing during SWS improved recall performance for the German translation equivalents of Dutch words, and interestingly also demonstrating that additional auditory input immediately after cueing abolished this beneficial effect (Schreiner et al., 2015). However, due to the linguistic similarity between Dutch and German, a large proportion of the novel words in both these studies were cognates in participants' native language (e.g., "soep" and "suppe"). Given that many second language learners are tasked with acquiring completely unfamiliar vocabulary words, our goal was to extend Schreiner and colleagues' result, testing whether TMR can boost vocabulary learning of entirely novel words. We also examined whether TMR might be effective over a relatively short afternoon nap, rather than overnight.

Participants in our study learned the meanings of a set of novel words, each paired with an associated sound, before taking an afternoon nap (Figs. 1 and 2). Next, half of the associated sounds were covertly presented during SWS. Participants were then tested on all vocabulary words upon awakening (see Fig. 3 for overview). Counter to our original hypothesis that TMR would improve vocabulary retention, there was no reliable effect of TMR on accuracy at the group level. However, memory results were systematically modulated by REM sleep.

2. Materials and methods

2.1. Participants

A total of 37 participants (mean age = 20.9 y, SD = 1.85 y; 23 female) were recruited for this study. All participants were neurologically normal, reported no known sleep disorders, and were native and/or highly proficient English speakers. They were asked to abstain from caffeine on the day of the experiment and to wake up 1 h earlier than normal. Of the 37 participants, 26 provided data for the analyses below (mean age = 20.7 y, SD = 1.28 y; 14 female). The other 11 participants were excluded from the sample for the following reasons: inability to present cues during sleep ($n = 9$), either because of insufficient sleep ($n = 5$) or because cueing attempts resulted in arousals ($n = 4$); computer malfunction which resulted in administering the incorrect version of the post-nap learning test ($n = 1$); participant declined to continue participation in study after initial learning procedure ($n = 1$).

2.2. Word-learning task and post-nap test

Participants were trained on the meanings of 60 novel vocabulary words, which they were informed were from an artificial foreign language. These words were actually not from any known language (see Supplementary Materials for exact words).

Two similar versions of this task were run. In one version of the task, termed the "Sound-Cues" version, environmental sounds associated with the novel words were presented during sleep (e.g., a meow sound). In a second version of the task, termed the "Word-Cues" version, the spoken novel words were presented during sleep. Previous TMR studies have used both types of cues during sleep—environmental sounds (e.g., Rudoy, Voss, Westerberg, & Paller, 2009; Oudiette, Antony, Creery, & Paller, 2013; van Dongen et al., 2012) and spoken words (Schreiner & Rasch, 2015; Groch et al., 2016)—although it is unclear whether one type of cue is more effective. By running these two task versions, we sought to determine whether environmental sounds or spoken words served as more effective cues for producing memory benefits. However, no significant differences were found between the task versions, and thus we combined subjects from both versions in all analyses. Of the 26 participants included in the analyses, 16 completed the Sound-Cues version and 10 completed the Word-Cues version. In both versions of the task, the learning procedures were similar. Participants learned the meanings of the novel words in three separate blocks, each containing twenty novel words. Each training block consisted of three phases. The two versions of the task are described below.

Sound-Cues version (Fig. 1). In this version of the task, participants were required to form three-way associations between novel written words (e.g., "dreep"), their assigned meanings or real-world referents (e.g., image of an apple), and semantically related environmental sounds (e.g., "crunch" noise of someone biting into an apple). The first phase of training involved familiarizing participants with the environmental sound cues by presenting each auditory sound simultaneously with its associated object picture (e.g., image of an apple and "crunch" noise). The purpose of this initial training phase was to facilitate the intended comprehension of the environmental sounds, which otherwise could sometimes be difficult to comprehend. Environmental sounds were approximately 500 ms in duration and each object-sound pair was presented twice.

In the second phase of training, participants were introduced to the novel word for each item. Each trial consisted of a picture of the object, the written novel word displayed below the object, and the associated environmental sound. The interval between each trial was approximately 3 s. Participants were instructed to learn the association between the novel word and the object. Each association was presented once. All novel words consisted of exactly 5 letters and followed the phonotactic and orthographic rules of English. Assignment of novel words to each object-sound pairing was randomized across participants.

In the third phase of training, participants performed a speeded recall task with graded cues for each word. On each trial, the environmental sound for the associated novel word was presented without the corresponding picture. Participants responded with a button press when they determined that they had mentally recalled the associated word. They then typed the word on a keyboard and received feedback on whether their response was correct or not. If no initial button-press response was made within 4 s, hints in the form of letters from the word were provided. One letter was revealed every 2 s, beginning with the first letter of the word. Participants performed a minimum of two graded recall task trials for each word. After a minimum of two presentations, once participants successfully recalled a given word within 4 s (prior to the onset of letter hints), the word was dropped from the learning procedure. Thus, as participants learned more words, each cycle of learning contained progressively fewer words, allowing participants to continue studying only the words that they had not yet successfully learned.

The post-nap test involved a similar procedure to the third phase of learning. Each item was tested once. Each trial began with the environmental sound. Again, participants responded with a button press when they determined that they had mentally recalled the associated novel word. If they failed to respond within
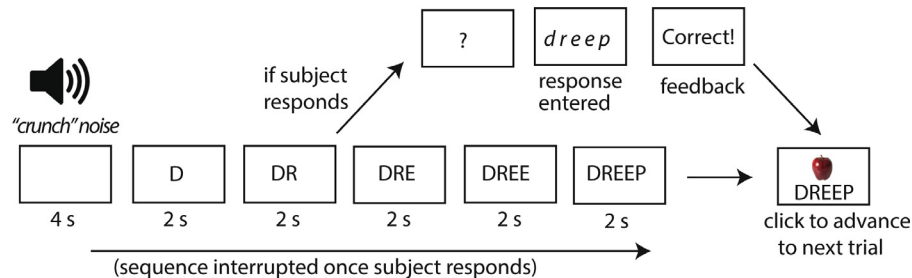
A Word Learning Task

Phase I: Sound Familiarization

"crunch" noise

Phase II: Novel Word Meaning Familiarization

"crunch" noise

DREEP

Phase III: Speeded Recall Task with Graded Cues

"crunch" noise

if subject responds

? | *d r e e p* | Correct!

response entered | feedback

| | D | DR | DRE | DREE | DREEP |
| 4 s | 2 s | 2 s | 2 s | 2 s | 2 s |

DREEP

click to advance to next trial

(sequence interrupted once subject responds)

B Post-Nap Test

"crunch" noise

if subject responds

?

d r e e p | Correct!

response entered | feedback

| | D | DR | DRE |
| 4 s | 2 s | 2 s | until subject response |

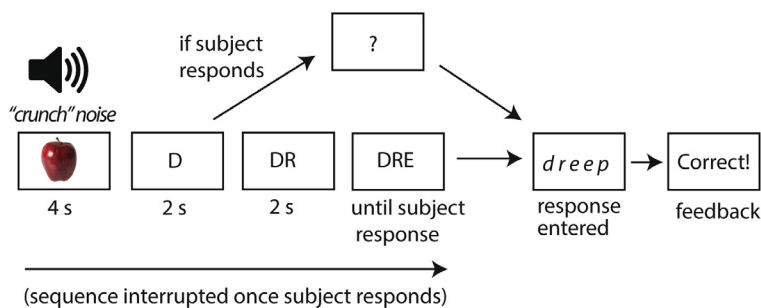(sequence interrupted once subject responds)

Fig. 1. Sound-Cues version of experimental task. Participants learned associations among written novel words, object images, and associated environmental sounds. The environmental sounds were used as cues during the speeded recall task and also presented covertly during the afternoon nap.

4 s, one letter of the novel word was presented every 2 s, up to a maximum of three letters. This procedure was designed to probe for partial word knowledge by providing a hint about the identity of correct responses when they could not be correctly recalled, allowing for greater sensitivity than a test without hints.

Word-Cues version (Fig. 2). The Word-Cues version of the task involved the same general procedure as the Sound-Cues version, but required participants to learn the meanings of spoken novel words rather than written novel words. All novel words were between 1 and 3 syllables in length, were recorded by a female native English speaker, and followed the phonotactic rules of English. Recordings ranged between 400 and 900 ms in duration.

In the first phase of learning, participants were exposed to a set of auditory novel words (e.g., "clambil"), prior to any meaning assignment, in order to familiarize them with the spoken words. Each word was presented once. In the second phase, the word was presented simultaneously with an image of an object and its English translation eq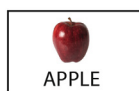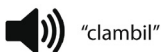uivalent written below. Participants were instructed to learn the associations between the novel words and their assigned meanings. Each word was presented once. Again, assignment of words to objects was randomized across participants. In the third phase, participants performed a speeded recall task with graded cues. On each trial, the novel auditory word was presented simultaneously with an image consisting of a randomized black and white pixelated mask, also known as "salt and pepper" noise. This pixelated mask was superimposed over (and completely obscured) the first three letters of the English translation equivalent. Participants were asked to respond via button press when they were able to recall the English translation equivalent. They then typed the word on the keyboard and received feedback on their response. If no response was made within 4 s, an image displaying the first three letters of the English translation equivalent was gradually revealed over the course of approximately 16 s by progressively reducing the intensity of the pixelated mask. As soon as the participant responded, this sequence was interrupted and the participant was asked to type
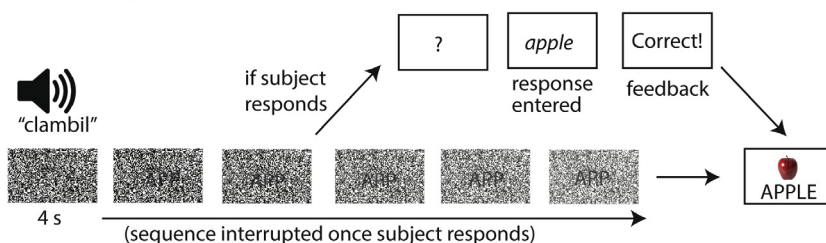
A Word Learning Task

Phase I: Novel Word Familiarization

🔊))) "clambil"

Phase II: Novel Word Meaning Familiarization

🔊))) "clambil"

APPLE

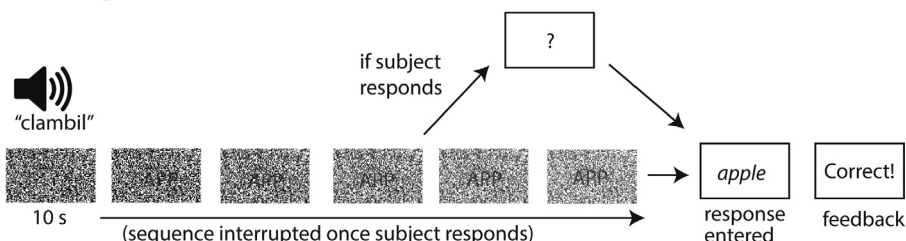*Phase III: Speeded Recall Task with Graded Cues*

Fig. 2. Word-Cues version of experimental task. Participants learned associations between spoken novel words and object images. The spoken words were used as cues during the speeded recall task and also presented covertly during the afternoon nap.
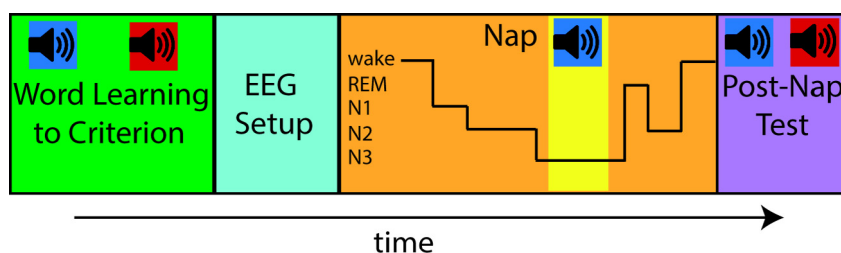

Fig. 3. Summary of experimental procedure. Half of the items during the word learning procedure were presented during the afternoon nap, and all were tested upon awakening.

the English equivalent. If no response was made, the first three letters of the word eventually became fully visible. The participant was then shown the associated object and the full English translation equivalent. The same learning criteria and drop-out procedure for individual words were applied as in the Sound-Cues version of the task.

The post-nap test involved a similar procedure to the third phase of learning. On each trial, participants were presented with an auditory novel word and asked to recall the English translation equivalent. If no response was made within 10 s, the first three letters of the English translation equivalent were gradually clarified over the course of the next 28 s, becoming partially though not fully visible by the end of the sequence. As in the Sound-Cues ver-

sion, this procedure was designed to provide fine-grained measures of participants' knowledge of the identity of learned words that could not be correctly recalled, without fully disclosing the correct response.

2.3. Procedure

The general procedure is summarized in Fig. 3. The experimental session began between 11 AM and 3 PM. Participants first completed the vocabulary-learning task, achieving the learning criterion (successful recall of each word prior to any hints) for all 60 novel words. Electrodes were then applied for standard sleep EEG recording and participants reclined on a fold-down bed with

a pillow and blankets in a quiet, darkened room to sleep for 90 min. Low-intensity white noise at ∼40 dB was present for the duration of the sleep period to dampen the influence of possible noise from outside the room and as well as to embed the cues. That is, cues were presented against an acoustic background of white noise in addition to the ambient noise in the building, rather than a background of complete silence; our intention was to acclimatize participants to low-intensity noise while they fell asleep, so that the onset of sound cues during SWS would be less likely to cause sleep arousals.

A computer algorithm was used to select 30 of the 60 possible items for presentation during sleep. Cued and uncued items were selected to closely match the following parameters, in order of decreasing priority: training block (1–3), number of presentations to reach criterion, cumulative number of correct responses, cumulative reaction times for correct responses, and reaction time to the final correct trial. Items that were subsequently assigned to the cued condition were presented an average of 3.67 times before reaching criterion, averaged 2.35 cumulative correct responses, had an average cumulative reaction time across correct trials of 12,794 ms, and an average final RT of 1780 ms. Items that were subsequently assigned to the uncued condition were presented an average of 3.65 times before reaching criterion, averaged 2.39 cumulative correct responses, had an average cumulative reaction time across correct trials of 12,455 ms, and an average final RT of 1822 ms. None of these parameters differed significantly between cued and uncued items (all p values > 0.25, two-sample t-test), and thus by these measures the two chief conditions of cued and uncued words were equally well-learned prior to the nap.

Sound-cue presentation began once indications of SWS were observed. Sound cues consisted of either environmental sounds or spoken auditory words, as described above. Stimulation was paused if signs of arousal were observed, and was restarted only if a stable pattern of SWS re-emerged. Stimulation was paused an average of 1.9 times (SD = 2.5) per participant. Across participants, an average of 150 sound cues were presented (range = 41–240). A minimum of one full cycle of cues (30 total) was required for participant inclusion, with a maximum of 8 cycles (240 cues) presented. Cues were presented every ∼8 s (Sound-Cues version) or every ∼5 s (Word-Cues version), which is in the general range of the stimulation rate in previous TMR studies (e.g., Rudoy et al., 2009; Oudiette et al., 2013; Creery, Oudiette, Antony, & Paller, 2015).

The nap period ended after ∼90 min (mean length of nap = 92 - min; SD = 5.3 min), except in one case in which the participant was allowed to sleep longer due to still being in SWS. After awakening, electrodes were removed and participants were given a brief 10–15 min break before completing the post-nap test. During the break, participants filled out a questionnaire reporting on the quality of their nap and then waited quietly.

2.4. EEG recording and analysis

EEG was recorded over the nap period from 21 tin electrodes mounted in an elastic cap, along with additional electrodes on the left and right mastoid, two electrooculogram (EOG) channels and one chin electromyogram (EMG) channel, using a 250-Hz sampling rate. Data were referenced online to the right mastoid and re-referenced offline to the algebraic average of the left and right mastoid. Scalp data were recorded at the following locations according to the 10–20 system: Fp1, Fpz, Fp2, F7, F3, Fz, F4, F8, C3, Cz, C4, T3, T4, T5, T6, P3, Pz, P4, O1, Oz, O2.

For sleep analyses, data from EEG and EOG channels were filtered with a bandpass from 0.5 to 30 Hz, and EMG data were filtered from 10 to 62 Hz. Sleep staging was conducted offline using standard criteria recommended by the American Academy

of Sleep Medicine, with 30-s EEG epochs scored as wake, Stage 1, 2, SWS or REM. Sleep staging was performed by two raters working independently. Our main sleep measures of interest were duration of SWS, duration of REM sleep, and total sleep duration. These three measures showed a high correspondence between the two sets of scores (duration of SWS: $r = 0.92$, $p < 0.001$; duration of REM: $r = 0.81$, $p < 0.001$; total sleep duration: $r = 0.84$, $p < 0.001$). For all discrepancies, the data were re-examined and a consensus was reached through discussion between the two raters.

2.5. Statistical analysis

Both accuracy and reaction time (RT) data were computed for each trial of the post-nap test. In the Sound-Cues version, only responses that exactly matched the novel word (i.e., with all 5 letters matching) were considered correct. In the Word-Cues version, participants were permitted to type in either the first three letters of the English word (e.g., "app") or the entire English word (e.g., "apple") when providing their response. This option was included to avoid unnecessary difficulty with spelling or typing, as some of the English translation equivalents were somewhat long (e.g., "electricity"). In the case where participants typed in the entire English word, minor spelling errors and typos were ignored, though these occurred very rarely (on average less than once per participant). RT was computed as the time from onset of the sound cue to the participant's initial button press. Trials where a correct response was provided prior to the onset of the hint procedure were considered correct "free recall" trials, whereas trials where a correct response was provided only after the onset of the hint procedure were considered correct "hint" trials. For each participant, we computed both the median RT to correct recall trials (which included only "free recall" trials), and to correct trials overall (which included both "free recall" and "hint" trials). Median RTs to correct trials are reported as a measure of central tendency within each condition (e.g., cued versus uncued), as a method to eliminate the influence of outliers (i.e., very long RTs). Overall accuracy was computed across both free recall and hint trials, weighting each trial equally. The *accuracy cueing effect* was calculated by subtracting overall accuracy in the uncued condition from overall accuracy in the cued condition.

3. Results

3.1. Behavioral performance

In the post-nap test, overall recall accuracy was 79.2% (SD = 16.1%) in the cued condition and 79.9% (SD = 13.3%) in the uncued condition. In the cued condition, 59.6% (SD = 22.7%) of the total number of trials were freely recalled, with an additional 19.6% (SD = 15.0%) correctly recalled following the hint procedure. In the uncued condition, 61.5% (SD = 18.8%) of trials were recalled, with an additional 18.3% (SD = 12.3%) correctly recalled following the hint procedure. Counter to our original hypotheses, there was no significant effect of cueing on overall accuracy, correct free recall rate, or correct hint rate (all p values > 0.41; paired t-tests).

Median RT to correct recall trials was 1581 ms (SD = 551) in the cued condition and 1540 ms (SD = 444 ms) in the uncued condition. Median RT to correct trials overall was 2227 ms in the cued condition (SD = 1353 ms) and 2226 ms in the uncued condition (SD = 1301 ms). There was no significant effect of cueing on either of these RT measures (both p values > 0.5, paired t-tests).

Performance during the learning task was quantified by the number of trials required to reach the learning criterion. Participants varied widely on this measure (mean = 248, range = 139–475, with 120 trials representing the fastest possible

learning), as some participants learned much more quickly than others. There was a significant negative correlation between number of trials to learning criterion and overall performance ($r = -0.51$, $p = 0.008$), such that participants who learned more quickly (requiring fewer trials to reach the learning criterion) also appear to have formed stronger memory representations, performing better overall on the post-nap test.

3.2. Effects of sleep architecture on cueing effects

Our chief sleep-related analysis examined whether sleep architecture (i.e., durations of different sleep stages) modulated the *accuracy cueing effect*. The *accuracy cueing effect* was computed as the difference in overall accuracy between the cued and uncued conditions, providing a measure of the accuracy benefit associated with TMR. Given previous evidence linking SWS and REM to memory consolidation effects (e.g., Walker & Stickgold, 2010; Diekelmann & Born, 2010), duration of SWS (SWS_{dur}) and duration of REM (REM_{dur}) were selected as *a priori* predictors in a multiple regression model, with the accuracy cueing effect as the dependent variable. Total sleep duration (total $sleep_{dur}$) was included as an additional predictor in order to control for total sleep time, allowing us to assess the specificity of sleep-stage effects. Finally, experimental version (Sounds-Cues versus Word-Cues) was included in the model in order to control for the possible influence of this effect.

Average sleep measures are shown in Table 1. A regression model with our four predictor variables (SWS_{dur}, REM_{dur}, total $sleep_{dur}$, and task version) significantly predicted the accuracy cueing effect [$F(4,21) = 3.41$, $p = 0.027$]. However, only REM_{dur} contributed to the model ($\beta = 0.40$, $t(21) = 2.06$, $p = 0.052$). SWS_{dur} ($\beta = 0.14$, $t(21) = 0.58$, $p = 0.57$), total $sleep_{dur}$ ($\beta = 0.28$, $t(21) = 1.08$, $p = 0.29$), and version ($\beta = 0.046$, $t(21) = 0.26$, $p = 0.79$) were not significant predictors and were subsequently excluded from the model. The resulting model with REM_{dur} as the remaining independent variable significantly predicted the cueing effect [$F(1,24) = 8.77$, $p = 0.007$; Fig. 4]. These results remained significant after excluding one participant who may be considered an outlier, due to obtaining an unusually large amount of REM sleep ($\sim$34.5 min, see Fig. 4; regression with REM_{dur} as sole predictor: $F(1,23) = 5.44$, $p = 0.029$). In addition, we replicated this analysis excluding participants who did not reach REM sleep ($n = 6$), and found that REM_{dur} continued to predict the accuracy cueing effect in this subset of participants ($F(1,18) = 5.45$, $p = 0.031$). In sum, duration of REM but not SWS predicted the accuracy cueing effect. SWS_{dur} and REM_{dur} did not significantly correlate ($r = 0.055$, $p = 0.79$).

The finding that task version did not have a significant impact on our original regression model suggests that cue type does not impact the relationship between sleep physiology and the accuracy cueing effect. Consistent with this finding, there was no significant difference in the accuracy cueing effect between participants run on the Sound-Cues version ($n = 16$; M = -0.21%, SEM = 2.7%) and on the Word-Cues version ($n = 10$; M = -1.3%, SEM = 4.7%; $t(24) = 0.24$, $p = 0.81$). Overall accuracy was also not significantly different between the two groups (Sound-Cues: M = 78.7%, SEM = 3.2%; Word-Cues: M = 81.0%, SEM = 5.0%, $t(24) = 0.42$, $p = 0.68$). There was also no significant difference in REM_{dur} between participants

in the two task versions ($t(24) = 0.73$, $p = 0.47$). In addition, as shown in Fig. 4, both groups showed similar correlations between the accuracy cueing effect and REM_{dur} (Sound-Cues version: $r = 0.53$, $p = 0.033$; Word-Cues version: $r = 0.50$, $p = 0.14$), though the correlation did not reach significance in the Word-Cues group, likely due to the smaller sample size. In sum, differences between the two task versions did not substantially influence interactions between TMR and sleep physiology.

In a follow-up analysis, we divided participants by median split based on REM_{dur}, revealing two distinct subgroups of participants. Participants who obtained greater amounts of REM (10 min or more; $n = 13$) showed a significant positive TMR effect [accuracy cueing effect = 6.15%; mean cued accuracy = 85.9%, SD = 9.8%, mean uncued accuracy = 79.7%, SD = 12.7%; $t(12) = 2.89$, $p = 0.014$, paired t-test]. In contrast, participants who obtained less than 10 min of REM ($n = 13$) showed a significant negative TMR effect [accuracy cueing effect = -7.43%; mean cued accuracy = 72.6%, SD = 18.7%; mean uncued accuracy = 80.0%, SD = 14.4%; $t(12) = -2.49$, $p = 0.028$]. Interestingly, performance between the two groups differed significantly only for cued items ($t(24) = 2.30$, $p = 0.035$), and not for uncued items ($t(28) = -0.048$, $p = 0.96$). This result suggests that REM sleep specifically impacted memory for items that had been previously cued, rather than having a global effect on memory performance. Participants from the two task versions were represented equivalently across the high and low REM_{dur} groups (both groups included $n = 8$ from the Sound-Cues Version and $n = 5$ from the Word-Cues Version).

Next, we tested whether REM_{dur} predicts the cueing effect for free recall and hint trials separately, computed as the difference in the number of correct free recall (or hint) trials between cued and uncued conditions. Interestingly, REM_{dur} did not predict the cueing effect for free recall trials ($F(1,24) = 0.37$, $p = 0.55$), but significantly predicted the cueing effect for hint trials ($F(1,24) = 5.16$, $p = 0.032$). This finding suggests that memories that have a weaker signal are more likely to benefit from a combination of TMR and subsequent REM sleep.

The number of stimulation pauses did not correlate with REM_{dur} ($r = -0.17$, $p = 0.40$), nor with the accuracy cueing effect ($r = 0.22$, $p = 0.91$), providing assurance that the negative cueing benefit of TMR in low-REM participants was not confounded by awakenings during cueing. There were also no significant correlations between the number of cues presented during sleep and REM_{dur} ($r = -0.16$, $p = 0.43$), or with the accuracy cueing effect ($r = 0.11$, $p = 0.59$). The number of cues presented during sleep correlated negatively with the number of stimulation pauses ($r = -0.40$, $p = 0.044$).

3.3. Other factors contributing to the accuracy cueing effect

Number of trials to criterion during learning did not correlate with the accuracy cueing effect ($r = 0.21$, $p = 0.30$) or with the cueing effect for free recall trials ($r = -0.20$, $p = 0.32$). However, this measure significantly correlated with the cueing effect for hint trials ($r = 0.46$, $p = 0.019$). Given that a larger number of trials during learning is indicative of weaker learning (as reflected by the negative correlation between number of trials to criterion and poorer overall performance on the post-nap test), this finding again suggests that weaker learning in our paradigm may be associated with greater potential TMR-related gains. This finding is consistent with

Table 1
Sleep measures ($n = 26$).

Awake	Stage 1	Stage 2	SWS	REM
19.7 (12.8)	12.9 (6.8)	22.2 (8.2)	26.9 (12.5)	10.3 (8.8)

Time (min) spent in different sleep and wake stages during 90-min nap (*SD* in parentheses).
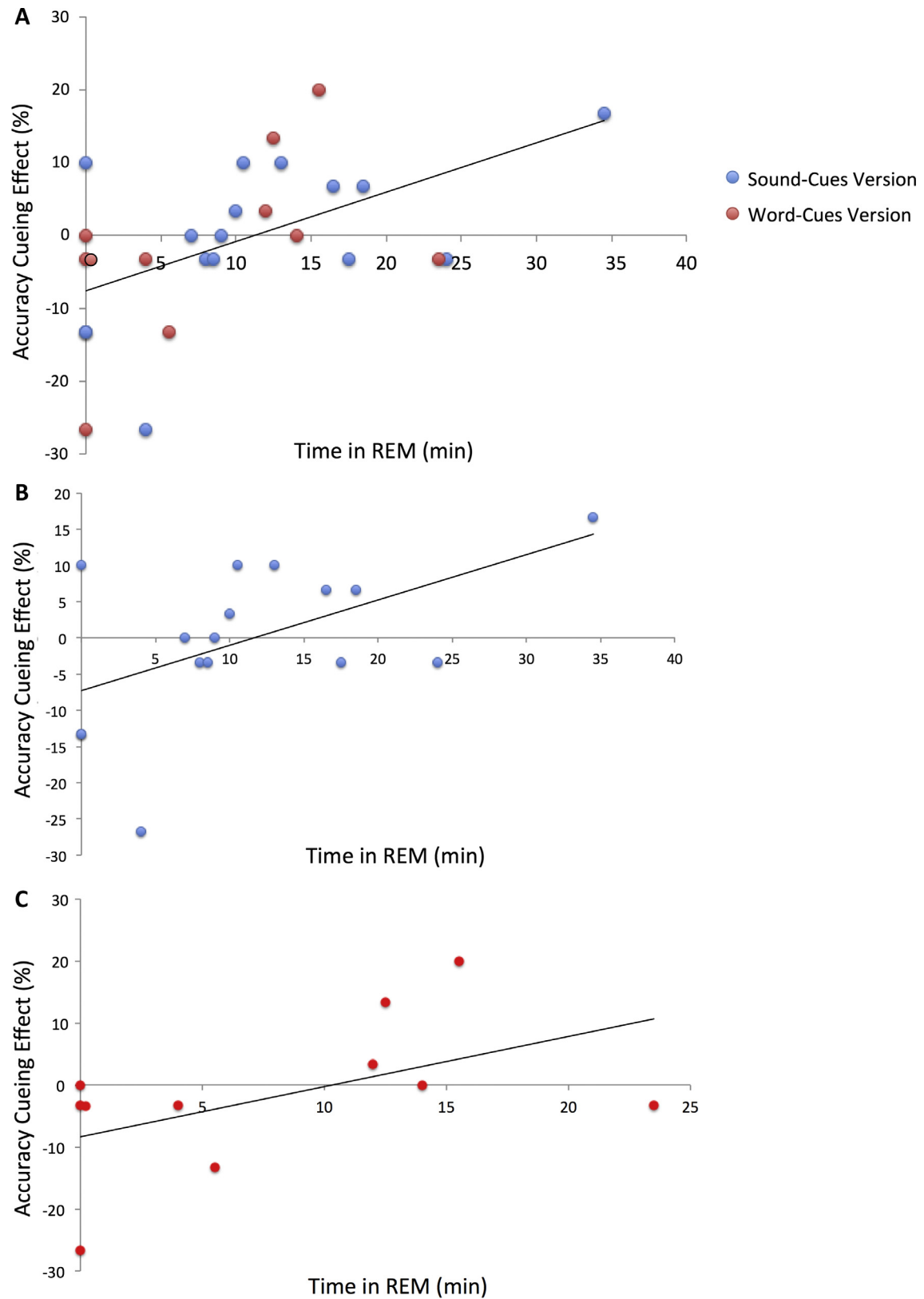
Fig. 4. Results of regression analysis showing relation between duration of REM sleep and the accuracy cueing effect, computed by subtracting overall accuracy in the uncued condition from overall accuracy in the cued condition. (A) Data from all participants, combined from both Sound-Cues and Word-Cues task versions. (B) Data from participants in Sound-Cues version alone. (C) Data from participants in Word-Cues version alone.

previous research demonstrating that weaker memories benefit more from consolidation during sleep (Drosopoulos, Schulze, & Born, 2007).

4. Discussion

This experiment was designed to investigate the influence of TMR on memory for newly acquired vocabulary words, in order to shed light on memory consolidation during sleep. However, rather than finding a straightforward enhancement in post-sleep memory performance for cued words compared to uncued words, as might be predicted based on prior results (Schreiner et al., 2015), we found that the influence of TMR on memory varied systematically with the duration of REM sleep.

Participants who obtained greater amounts of REM sleep in the latter portion of the afternoon sleep period showed the expected memory benefit for cued items, whereas participants who obtained less REM sleep showed the opposite pattern of results, with better accuracy for uncued items. We suggest that for certain types of learning such as novel vocabulary acquisition, reactivation during SWS may be maladaptive if not followed by REM. Subsequent REM sleep may be needed to stabilize and integrate reactivated memory traces into pre-existing networks.

These results highlight an advantage of studying afternoon sleep. During nocturnal sleep, periods of SWS are commonly followed by REM, whereas REM periods are more variably achieved during an afternoon nap. This characteristic of afternoon sleep allowed us to make use of cross-subject variability in REM to reveal evidence about its function that might not be apparent when all participants achieve typical amounts of REM sleep.

4.1. TMR effects may be modulated by REM sleep for highly-integrative learning

Our finding that cueing effects were modulated by REM sleep duration—with cued items showing *poorer* performance compared to uncued items when little to no REM sleep was obtained—was not expected *a priori*. This result contrasts with previous findings showing that TMR often results in a relative boost in memory performance. For example, presenting cues during short periods of afternoon sleep (from 40 min to 3 h) has produced selective benefits for visual-spatial memory (Rudoy et al., 2009; Diekelmann et al., 2011, 2012), skill learning (Antony et al., 2012; Schönauer et al., 2014), and training in social-bias reduction (Hu et al., 2015). Given that cueing effects were significant across participants who likely obtained variable durations of REM sleep, these prior results do not implicate REM sleep as playing a critical role in modulating cueing effects. Indeed, several of these studies reported significant cueing benefits even when no REM sleep was obtained by any participant (Rudoy et al., 2009; Diekelmann et al., 2011, 2012).

Although a number of different parameters or features may have varied across these studies, type of memory is likely one of the most important factors to consider; REM may modulate TMR effects for novel vocabulary learning, but not for these other types of memory. One possibility is that REM plays a more important role in stabilizing memories that strongly depend on integration with pre-existing knowledge. This idea fits with the general proposal that REM sleep facilitates the integration of new memories with older memories, forming associative networks (e.g., Ambrosini & Giuditta, 2001; Walker & Stickgold, 2010). Vocabulary acquisition is a prime example of learning that entails this type of integration, requiring the incorporation of novel word meanings into an existing semantic network for known concepts. For example, to learn that "clambil" means "apple," a new relationship must be formed

between the new word "clambil" and the previously learned multisensory and multidimensional concept for apple. In contrast, previous experimental tasks that have revealed TMR benefits in the absence of REM sleep do not critically require the same degree of integration with existing memories. For example, learning the locations of card-pairs (Diekelmann et al., 2011, 2012), the locations of object images (Rudoy et al., 2009) or learning to perform a melody (Antony et al., 2012; Schönauer et al., 2014) are essentially learning tasks that can occur in relative isolation, with less dependence on other relevant knowledge. This interpretation also fits with a recent study by Tamminen et al. (2017), who studied the effects of TMR on the integration of new memories using a lexical competition task, in which newly learned spoken words (e.g., *cathedruke*) compete with similar-sounding existing words (e.g., *cathedral*). Converging with the present findings, TMR did not modulate lexical competition overall, but changes in lexical competition to cued words was predicted by the time spent in REM sleep during a 90-min afternoon nap. Negative TMR effects were also observed when participants obtained little or no REM sleep. Taken together, both our findings and Tamminen and colleagues' findings suggest that the impact of TMR on learning that requires integration, such as lexical integration and vocabulary acquisition, is mediated in part during REM sleep.

We suggest that in general, reactivation during SWS may act to both strengthen a memory while simultaneously placing the memory in a modifiable or plastic state. This transient destabilization would allow a new memory to be more readily linked with other information (Rasch & Born, 2007), but may at the same time make the memory temporarily vulnerable to interference or contamination. Subsequent REM sleep may function to close this window of plasticity by stabilizing and integrating the memory into long-term memory networks. However, if no REM sleep occurs, the memory may be modified or influenced by existing related memories, or linked with potentially irrelevant information, placing it at greater risk of contamination or distortion.

Given the current findings as well as prior TMR results, an intriguing possibility is that memory reactivation during SWS has different consequences depending upon the degree to which the memory requires integration with previous knowledge. That is, the extent to which contamination from older, related memories occurs may depend upon the type of learning. Isolated types of knowledge may be relatively resistant to distortion, as they share few connections with other memories, making interference from related information less likely to occur. In contrast, for highly inter-connected memories (such as vocabulary items) that have strong links to established schemas and semantic networks, contamination from related memories may be much more frequent, likely, or detrimental. This outcome may then lead to a decline in subsequent memory performance, depending on what is tested, rather than the boost in memory accuracy that is observed for more isolated types of knowledge.

The hypothesis that reactivation during SWS without sequential REM sleep may destabilize memories was tested previously in the context of spatial memory, using a card-pair location learning paradigm (Diekelmann et al., 2011). Spatial memories were reactivated by presenting associated odor cues either during SWS or wakefulness, followed by an interference task to probe memory stability. Contrary to their original prediction that memory reactivation during SWS would destabilize the memory trace, Diekelmann and colleagues found that reactivation during SWS enhanced memory performance compared to a control vehicle odor, without requiring REM sleep. In contrast, reactivation during wake led to a decrease in memory performance. Reactivation during wake may have destabilized the associated memories, or alternatively may have blurred the temporal distinctiveness of the original learning and the interference learning, thereby increasing

the likelihood of intrusions. Although Diekelmann and colleagues' original hypothesis—that reactivation during SWS may transiently destabilize a reactivated memory, with subsequent REM sleep then potentially leading to strengthening—was not supported by their own results, it is supported by the current findings. Taken together with Diekelmann and colleagues' findings, our results additionally suggest that the role of SWS and REM in stabilizing and integrating memories could depend upon the nature of learning. Unrelated or unconnected knowledge that can be learned in isolation may not be susceptible to potential interference or contamination when reactivated during SWS, whereas highly associated or connected memories may require subsequent REM sleep after SWS reactivation to be strengthened and improved.

In contrast to the current study, which did not reveal significant overall cueing benefits for vocabulary words at the group level, Schreiner and Rasch (2015; see also Schreiner et al., 2015) did find significant TMR effects on vocabulary learning, as reviewed in the Introduction. One factor that may partially account for these divergent results is that the novel words used in our study may have been more prone to interference or contamination than the novel words used by Schreiner and Rasch. Whereas our words had no pre-existing relationship to their translation equivalents (e.g., "clambil – apple"), many of the word pairs used by Schreiner and Rasch were cognates and phonetically related (e.g., "soep" and "suppe"). Because Schreiner and Rasch's word pairs were less easily confusable, reactivation during SWS may have been more likely to strengthen these associations, whereas in the present study reactivation may have created or solidified additional linkages to incorrect concepts or translation equivalents, resulting in a net destabilization rather than a net strengthening. That Schreiner and Rasch found significant cueing benefits whereas the present study did not could also be at least partially attributed to the greater and less variable duration of REM sleep obtained by participants in Schreiner and Rasch's study compared to participants in our study (Schreiner & Rasch: mean REM duration = 22 min ± 3 min; current study: mean REM duration = 10 min ± 9 min). Whereas several participants in our study obtained no REM sleep at all, it is likely that all or virtually all participants Schreiner and Rasch's study obtained at least some REM sleep, given that the experiment occurred over the first half of the night rather than during a short afternoon nap. Taken together with the current results, these findings are consistent with the idea that REM sleep plays a role in stabilizing memories that highly depend on integration.

4.2. TMR effects may be modulated by level of encoding

Whereas type of learning is one factor to consider, another factor that may have differed between our study and previous studies is the strength of memory encoding. In the present study, our learning criterion required participants to successfully recall each target word at least once, in the absence of any hints, before being allowed to move on to the next part of the study. This individually-titrated learning procedure involved presenting a minimum of three rounds of exposure to all word pairs and likely produced relatively strong memory encoding. By comparison, the vocabulary learning procedure of Schreiner and Rasch (2015) involved only two learning rounds, regardless of individual performance, followed by a final test in which correct recall averaged 50% (range = 33–68%). The TMR procedure was then applied to 30 words that the participant correctly recalled, and 30 words that the participant did not correctly recall, such that half of the cued learned words had never actually been successfully recalled prior to the sleep portion of the study. Moreover, the remaining words were selected for the uncued condition and thus were not always closely matched. In contrast, cued words in our study were all

successfully recalled at some point prior to the sleep phase of the experiment, and thus the corresponding encoding may have been stronger overall.

In the present data, there were empirical indications that (1) TMR was more effective for slower/weaker learners (as demonstrated by the correlation between the number of trials to learning criterion and the cueing effect for hint trials), and that (2) memories with a weaker signal were more likely to benefit from a combination of TMR and subsequent REM sleep (as demonstrated by the finding the REM_{dur} predicted the cueing effect for subdivided hint trials but not for subdivided free recall trials). However, participants made relatively few correct hint responses (mean = 20%), such that cueing effects for hint trials were quite noisy, and so the corresponding hint-trial results require further substantiation.

Consistent with the present findings, previous research has shown that cueing benefits are maximal when pre-sleep recall accuracy is neither too good nor too poor (Creery et al., 2015) and that consolidation effects in general are stronger for weaker memories (Drosopoulos et al., 2007). Taken together, these observations tentatively suggest that a subset of participants in our study may have encoded items too strongly to show significant benefits of TMR. If all learners in the present study had encoded items more weakly—perhaps at a level comparable to that in the Schreiner and Rasch study—it is possible that an overall cueing benefit may have been observed, and that this overall benefit may have been further enhanced by subsequent REM sleep. This speculation will require further experimentation to verify.

4.3. Role of SWS and REM sleep in the consolidation of declarative memory

Our results have implications for the role of SWS and REM sleep in the consolidation of declarative memory. A popular idea in the earlier literature in this area was that SWS benefits consolidation of declarative or explicit information, whereas REM sleep benefits implicit knowledge (e.g., Yaroush, Sullivan, & Ekstrand, 1971; Fowler, Sullivan, & Ekstrand, 1973; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Marshall, Helgadottir, Molle, & Born, 2006; Yordanova et al., 2008; Plihal & Born, 1997, 1999). For example, Plihal and Born (1997, 1999) demonstrated that early SWS-rich sleep selectively benefits declarative memories, such as word pairs and spatial information, whereas late REM-rich sleep selectively improves procedural or implicit knowledge, such as mirror tracing and word-stem priming. Sleep deprivation studies provided converging evidence for this idea. As reviewed by Smith (2001), a number of studies have consistently shown that REM sleep deprivation impairs performance on procedural memory tasks, such as the Tower of Hanoi task, but not declarative memory tasks, such as word recognition and visual-spatial learning. However, other studies have shown that SWS can also improve procedural or skill learning (Antony et al., 2012; Gais, Plihal, Wagner, & Born, 2000; Huber, Ghilardi, Massimini, & Tononi, 2004; Aeschbach, Cutler, & Ronda, 2008) and that REM sleep can improve explicit memory (Fogel, Smith, & Cote, 2007; Rauchs et al., 2004). In a recent review of the literature, Ackermann and Rasch (2014) concluded that the idea that SWS benefits declarative memory while REM sleep benefits nondeclarative memory is "too much of a simplification to explain the diverse data on sleep and memory."

Our results support this more nuanced view of SWS and REM, providing evidence for a complementary role of SWS and REM sleep in consolidation of novel vocabulary words, a type of declarative memory. We found that vocabulary words that are reactivated during SWS show improvements in memory consolidation only if followed by an adequate period of REM sleep. Thus, these results support the view that REM sleep after SWS plays a sequential role in memory processing (e.g., Diekelmann & Born, 2010;

Ficca & Salzarulo, 2004), which fits intuitively with the observation that periods of REM naturally follow periods of SWS during nocturnal sleep. Our findings also show that these processes may be particularly important for vocabulary learning. It has been suggested that one factor influencing whether REM sleep contributes to consolidation of declarative memory is the complexity of learning, with REM playing a larger role in the consolidation of more complex declarative memories (cf. Rasch & Born, 2013). Vocabulary learning requires accessing semantic representations, which may require deeper conceptual processing than encoding simple verbal materials such as lists of known words or word pairs, thus representing a more complex form of declarative memory that may be partially consolidated through REM sleep.

5. Conclusions

Integration of novel information with existing knowledge is a key component of most types of learning. The level of integration required may critically modulate the contributions of SWS and REM sleep to memory consolidation. Our results provide novel evidence that vocabulary memories benefit optimally from a succession of SWS and REM sleep, and that integration is mediated by REM sleep (e.g., Diekelmann & Born, 2010; Giuditta et al., 1995; Ambrosini & Giuditta, 2001; Walker & Stickgold, 2010). These results also have important implications for future TMR studies, suggesting that sleep architecture interacts critically with cueing effects, at least for some types of learning. Finally, these findings suggest that consolidation of novel vocabulary items depends upon both SWS and REM sleep, an idea of practical importance for learners of both first and second languages.

Acknowledgments

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nlm.2017.07.001.

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