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No effect of vocabulary reactivation in older adults☆

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ABSTRACT

Quality of memory and sleep declines with age. However, the mechanistic interactions underlying the memory function of sleep in older adults are still unknown. It is widely assumed that the beneficial effect of sleep on memory relies on reactivation during Non-rapid eye movement (NREM) sleep. Targeting these reactivations by cue re-exposure reliably improves memory in younger participants. Here we tested whether the memory reactivation mechanism during sleep is still functional in old age. For this purpose we applied targeted memory reactivation (TMR) during NREM sleep in healthy adults over 60 years and directly compared the results to a group of younger participants. In contrast to young participants, older adults' memories did not generally benefit from TMR during NREM sleep. On the oscillatory level, successful reactivation of Dutch words during sleep did not reveal the characteristic increases in early theta activity and frontal spindle activity previously reported in young participants. Only in a later time window, theta oscillations were similarly increased during successful cueing for both young and older participants. Our results suggest that reactivating memories during sleep might be possible also in older adults. However at the same time this reactivation by TMR does not necessarily lead to a strengthening of memories across sleep as in younger participants. Further studies are needed to examine a potential loss of functionality of memory reactivation for consolidation during sleep in older adults.

1. Introduction

Aging is associated with a decrease in sleep quality. A meta-analysis of Ohayon et al. (2004) demonstrated that sleep becomes more fragmented, shorter and shallower in older adults. Sleep and particularly slow-wave sleep (SWS) is considered critical for optimal consolidation of long-term memories (e.g., Alger et al., 2012; Diekelmann and Born, 2010; Marshall and Born, 2007). As memory formation also declines with age, several authors have proposed a link between the change in sleep quality and memory with aging (Buckley and Schatzberg, 2005; Hornung et al., 2005). Interestingly, according to a recent extensive literature review by Scullin and Bliwise (2015), the empirical evidence for this link is rather inconsistent. While some studies reported that age-related decreases in SWS predict declines in memory consolidation (Backhaus et al., 2007; Mander et al., 2013; Westerberg et al., 2012), others observed no or even negative relationships between SWS and memory with age (Cherdieu et al., 2014; Mawdsley et al., 2014; Mazzoni et al., 1999; Scullin, 2013). Furthermore, Wilson and colleagues reported similar benefits of sleep for memory in three age groups (i.e. 20–34 y, 35–50 y and 51–70 y), in spite of strong differences in sleep quality and SWS (Wilson et al., 2012). And while some studies show benefits of sleep for memory in old and young groups (Aly and Moscovitch, 2010), several others report no evidence of a beneficial role of sleep in older compared to younger subjects (Scullin, 2013; Scullin et al., 2017). Finally, some researchers have suggested to include more detailed topographical information to reveal specific associations between SWS and memory in the elderly (Mander et al., 2017). Thus, the association between sleep and memory in old age is still largely unknown.

On a mechanistic level, it is widely assumed that the beneficial role

Abbreviations: N1, N2 and N3, stages 1–3 sleep; SWS, slow-wave sleep; SWA, slow-wave activity; REM, rapid eye movement sleep; NREM, non-rapid eye movement; TST, total sleep time; TMR, targeted memory reactivation

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of sleep for memory relies on a spontaneous reactivation of memory traces during SWS (Diekelmann and Born, 2010; Pavlides and Winson, 1989). According to the active system consolidation hypothesis, recently acquired memories are repeatedly reactivated during subsequent sleep. This reactivation is orchestrated by a fine-tuned interaction between cortical slow waves (< 1 Hz), thalamo-cortical spindle activity (~ 11–16 Hz) and hippocampal sharp-wave ripple activity (100–300 Hz), and support the gradual redistribution or system switch (Kitamura et al., 2017) of memories from temporary storage sites to a long-term integration in cortical memory networks. Interestingly, Gerrard et al. (2008) have already shown that although reactivation of the activity pattern during sleep was preserved in aged rats, their temporal order was impaired as compared to younger rodents (Gerrard et al., 2008). Thus, one could hypothesize that while the reactivation mechanism in terms of simple cell pair correlations itself remains stable, efficacy and functionality for memory gradually declines with age. This process could in theory be independent of the decline in general sleep quality. Alternatively, one could assume that the reactivation mechanism remains completely unaffected by age, and the impaired efficacy is solely due to the reduction in sleep quality and amount of slow-wave activity (SWA). Limiting the latter interpretation of results is a current study done by Helfrich et al. (2018): They showed that in older adults the coupling between sleep spindles and slow oscillations' up-state was physiologically partially intact, but temporally disrupted. The fact that spindles peaked earlier in the slow oscillation cycle in older adults was related to impaired memory consolidation of a hippocampus-dependent task. These results favor the conclusion that it is not SWA per se, but rather the mechanistic level which might reduce overnight memory consolidation effects in older adults.

In this study, we started to test the functionality of memory reactivation during sleep for memory formation in older adults. Therefore, we applied a method called targeted memory reactivation (TMR). It is based on finding that the spontaneous memory reactivations happening during sleep can be induced by externally presenting learning-related cues during sleep. In younger participants, several studies from our lab and others have now reliably established that re-exposure to memory cues during NREM sleep improves later retrieval performance (Antony et al., 2012; Rasch et al., 2007; Schreiner and Rasch, 2015). In addition, successful memory reactivation (i.e. the difference between later remembered vs. later forgotten stimuli after targeted memory reactivation (TMR) during sleep) is characterized by specific increases in oscillatory power in the theta band (ca. 6 Hz) and spindle band (ca. 13 Hz) (Groch et al., 2016; Lehmann et al., 2016; Oyarzún et al., 2017; Schreiner et al., 2015). According to our working model, increase in the theta band might reflect successful reinstatement of memory traces by cueing during sleep, whereas increased activity in the spindle band relates to processes of integration and stabilization of memories after reinstatement of the memory trace by the cue (Schreiner and Rasch, 2017). In the current study, we applied our established TMR paradigm using Dutch-German vocabulary to healthy participants over 60 years and examined the oscillatory correlates of successful reactivation during sleep. We compared the results to a subgroup of young participants reported in Schreiner et al. (2015). Based on the initial findings in rodents, we hypothesized that the behavioral benefit of reactivating memories in older adults is reduced as compared to younger participants. In addition, if mere pattern reactivation was preserved also in humans, we expected this to manifest in intact theta responses during successful reactivation, indicating successful reinstatement of memories after cue re-exposure during NREM sleep. In contrast, spindle timing is disrupted in older adults (Helfrich et al., 2018) and behavioral effects of cueing are missing when done during REM sleep where no spindles appear (Lehmann et al., 2016). Based on those results, we predicted lacking or reduced spindle responses suggesting that despite successful reinstatement by the cue, memory traces are less efficiently stabilized and integrated after their reactivation in older participants.

2. Materials and methods

2.1. Subjects

A total of 23 healthy, German-speaking older adults (n = 8 males, ranged 62–83 years, mean age of 71.00 ± standard deviation [*SD*] of 5.86) took part in the experiment. None of them had intercontinental flights or shiftwork within eight weeks before participation. On the experimental day, they refrained from drinking alcohol or caffeine and got up before 8 a.m. None had any knowledge of Dutch. All participants were included in the analyses of the behavioral memory effect and sleep parameters. As n = 8 participants did not experience memory gains or losses after cueing, they were excluded from the oscillatory analyses. The sample then consisted of n = 15 participants (69.3 ± 5.6 years, 12 females). For participating in both sessions, participants received 120 CHF. The Ethics Committee of the Faculty of Philosophy of the University of Zurich approved the study. All participants signed a written consent prior to participation.

We compared our findings in older adults with a group of younger adults (n = 27; 19 females; aged 18–28; mean age of 22.0 ± 2.7 years) included in Exp. 1 and 2 of Schreiner et al. (2015). Similar to older adults, n = 7 younger participants had to be excluded from the oscillatory analyses due to a limited amount of trials (final sample gains/losses: n = 20 younger participants; mean age 22.7 ± 2.6 years, 13 females). The group of younger participants was chosen for the following reasons: a) it consists of a replication of our original findings reported in Schreiner and Rasch (2015); b) the learning task and cueing procedure very closely resembled the task used in older participants (see task description) and c) the sample size was comparable to the sample size in older participants.

2.1.1. Sample size and power calculation

The effect size in our first study on Dutch vocabulary TMR was large (d_z > 1) on the level of memory performance (Schreiner and Rasch, 2015). As data are known to be more variable in older participants, we did our a-priori sample size estimation with a large effect of d_z = 0.8 (Rasch et al., 2014). N = 23 participants are needed to find an effect of d_z = 0.8 with a power of 1-β > 95% (two-tailed).

In addition, we also used a large effect of d = 0.8 to estimate between-group effects size in old versus young adults, based on the meta-analysis of Old and Naveh-Benjamin (2008) (average effect size of age effects in associative memory: d = 0.92). With our sample of n = 23 old and n = 27 young adults, the statistical power of achieving an effect of d = 0.8 is 1-β > 85% (one-tailed testing). For testing the interaction between age group (young vs. old) vs. cueing (cued vs. uncued words), the sample size was even sufficient to detect medium effect sizes (f = 0.25, rho (cued-uncued) = 0.4; one-tailed: 1-β > 90%). For old vs. young comparisons with respect to memory, it is legitimate to use one-tailed testing to increase statistical power to detect age effects as older adults are expected to perform worse than younger adults. Thus, we had sufficient statistical power to a) replicate a potential benefit of TMR in older participants and b) find an age effect of TMR if it exists. Power calculations were done with G*Power 3 (Faul et al., 2007).

2.2. Procedure

The participants were invited to two sessions which took place in the sleep laboratory. The first session started at 9:30 p.m. with the informed consent, some questionnaires (one was about their consumption of nicotine, caffeine, alcohol and drugs on the same day and the day before. The other asked for their sleep behavior on the previous day and their knowledge of Dutch on a scale from 1 (none) to 5 (very good), *mean* ± *SD*: 1.04 ± 0.2) and the attachment of the electrodes. Subjects were then allowed to go to bed and sleep until 6 a.m. This adaptation session aimed at familiarizing the subjects with the laboratory and the EEG electrodes. The second session was the experimental

night and started at 9 p.m. with the same questionnaire about caffeine, alcohol and drug consumption and the EEG attachment. Before participants could go to bed, they learned 60 vocabulary pairs which were consecutively presented. Thereafter, two feedback and one final recall trial without feedback were presented, the latter measuring presleep memory performance. Half of the correctly recalled and half of the incorrect or not remembered words were randomly selected for nocturnal presentation. The volume for word replay by night was individually calibrated according to the hearing threshold test. Subjects were then allowed to fall asleep. As soon as stable NREM sleep (sleep stages N2 or SWS) appeared, reactivation was started, beginning with 5 repetitions of a test-word increasing in volume to adapt to the later reactivation volume in order to reduce the risk of awakening subjects. After a minimum of 3 h of sleep and 90 min of reactivation, subjects were awakened. This procedure was in line with Schreiner et al. (2015) and enabled cueing during the night half with a larger amount of NREM than REM sleep. To overcome sleep inertia, subjects were allowed to go to the toilet, were offered a drink and filled in a sleep quality questionnaire (SF-A, Görtelmeyer, 2011). After 20 min, they recalled all the words again. Again, no feedback was provided. Thereafter, they were allowed to return to bed and sleep until 6 a.m. (see Fig. 1A for the procedure of the experiment).

2.3. Hearing threshold level test

To individually adapt the nightly volume of replayed vocabulary, a hearing threshold level test was done. A test-word was repeatedly presented over the loudspeakers which were placed in a similar distance to the subject as during later sleep. The volume of the word was regulated down and participants were asked to increase the volume until they could hear the voice. The loudness was measured with a decibel measure and the value was noted. Then, the participants were asked to reduce the volume until they could hardly hear the spoken word. Again, volume was measured and noted. This procedure was repeated three times. The mean from these six values was taken as hearing threshold level. During the experimental night, the words were presented with a volume of 15 dB above this threshold. Mean volume with which the words were presented was 71.16 ± 5.58 dB.

2.4. Vocabulary task

We used the vocabulary learning task as described by Schreiner and Rasch (2015). The Dutch words were presented acoustically via loudspeakers, followed by a fixation cross on the screen (500 ms). Subsequently, the corresponding German translation was presented in black font on the white screen for 2000 ms. A blank screen separated the trials (2000–2200 ms). Subjects were asked to memorize as many words as possible. To achieve a similar presleep learning level as in younger adults, we adapted the difficulty of the task by reducing the word list to 60 and by including an additional feedback learning trial. In those trials, a question mark appeared instead of the German translation after the spoken Dutch word and the fixation cross. Subjects were asked to name the corresponding translation or to say “next” in case they did not remember the word. Feedback was given by presenting the correct answer. The fourth iteration, in which no feedback was provided, was taken as presleep recall performance. The learning performance level before sleep was on average 61.02% out of the 60 words, indicating a medium task difficulty, excluding ceiling or floor effects.

After a minimum of 90 min of reactivation, subjects were awakened and recall was again tested by presenting the Dutch word and asking the participant to give the German translation. Again, no feedback was provided. The order in which the words were recalled was different across both recall phases. The relative performance level of nocturnal recall was measured by setting presleep performance to 100%. After post-sleep recall, words remembered before but not after sleep were classified as losses while those remembered after, but not before sleep were defined as gains.

The procedure of younger adults is described in detail in Schreiner et al. (2015). In short, younger adults learned 120 Dutch-German word pairs. Forty word-pairs from one reactivation category (see below) were disregarded, leaving 80 word-pairs for the current analysis. In the first learning round, both words were consecutively presented via loudspeaker including an inter-stimulus interval of 200 ms and an inter-trial interval of 1000–3000 ms. The second (cued recall + correct feedback) and third round (cued recall without feedback) corresponded to the two last learning rounds of older participants (see above).

2.5. Reactivation of vocabulary

After the last learning trial, an automatic MATLAB algorithm randomly extracted 50% of all correctly recalled and 50% of all incorrect or not recalled words during this last learning trial. Thus, 30 words were individually chosen for replay during later sleep (i.e., “cued” words) while the other 30 were not presented during sleep (“uncued” words). The replayed words thus consisted of individually differing proportions of previously recalled and non-recalled words. Only the Dutch words, without their German translation were presented via loudspeakers during sleep. During reactivation, one word appeared every 3.8–4.2 s in a randomized order, resulting on average in ca. 34 exposures per word. Sleep was scored online and reactivation was immediately stopped as soon as indications of REM sleep, arousals or awakenings appeared. Postexperimental offline sleep scoring confirmed that on average > 98% of the words were correctly presented during stage N2 or N3 sleep.

Reactivation procedure in younger adults is described in detail in Schreiner et al. (2015). Shortly, the 120 vocabularies were assigned to one of three categories, namely “cued, uncued” and “cue + feedback”. As in older participants, an automatic MATLAB algorithm randomly extracted correctly and incorrectly recalled words for each category. We disregarded the category “cue + feedback” in the current analysis, as older participants had only a “cued” and “uncued” word category. Thus, from the remaining 80 word-pairs, 40 words were individually chosen for replay during later sleep (i.e., “cued” words) while the other 40 were not presented during sleep (“uncued” words). During reactivation, one word appeared every 2.8–3.2 s (excluding 1 s of word presentation, thereby matching the inter-stimulus interval used in the old adults group of 3.8–4.2 s) in a randomized order, resulting on average in ca. 17 exposures per word.

2.6. Polysomnographic recordings

Electromyographic (EMG), electrocardiographic (ECG), electrooculographic (EOG), and electroencephalographic (EEG) electrodes were attached for polysomnography. Impedances did not exceed 80 kΩ. High density EEG was recorded with a 128 channels Geodesic Sensor Net (Electrical Geodesics, Eugene, OR) and a sampling rate of 500 Hz. For sleep scoring, data was filtered according to the settings suggested by the American Association of Sleep Manual (AASM). Those include a low frequency filter at 0.3 Hz and a high frequency filter at 35 Hz for the EEG electrodes. The EMG signal was filtered between 10 and 100 Hz. Two independent sleep scorers visually scored 30 s segments of sleep to define the stages 1–3, REM sleep, and wakefulness offline and according to standard criteria (Iber et al., 2007). Derivations F4, C4, O4, HEOG, VEOG, and EMG were used therefore. A third sleep expert was consulted in case of disagreement. For further analyses, segments with sleep stages 2 and 3 were included only to perform analyses only on those reactivations which occurred in the correct sleep stage (i.e. NREM).

2.7. EEG data analysis

Preprocessing was done with Brain Vision Analyzer 2.1 (Brain Products, Gilching, Germany). The electrodes were re-referenced against the mean of the mastoids (electrodes 100 and 57) and filtered (low-pass filter: 0.1 Hz; high pass filter: 35 Hz). Only segments scored as N2 and N3 were selected in order to exclude possible reactivations administered in a wrong sleep stage. Segments were built within -1000–4000 ms around the cues. Artefacts were excluded semi-manually. Voltage differences larger than 400 μV within an interval of 200 ms were automatically detected. Those were afterwards screened and deleted manually.

2.7.1. Wavelet-analysis

The wavelet analyses were performed with fieldtrip (Oostenveld et al., 2011) after preprocessing. Here, condition based segments were created according to overnight gains and losses, where effects on younger adults had been most pronounced, each beginning 1000 ms before the cue and ending 4000 ms after the reactivation. As not each participant had gained or lost words, the sample in which we could analyze gains and losses was reduced (n = 15) compared to the main sample (n = 23). On average, 47.07 ± 7.44 gains and 129.07 ± 15.24 losses entered the oscillatory analyses in older adults. In younger adults, analyses based on 32.5 ± 2.08 gains and 39.95 ± 5.13 losses. We selected a time window of -500 to −100 ms before the reactivation cue that served as the baseline for the calculation of the relative power change. The values thus represent power changes ranging from 0 to 1. For statistical analyses, these relative power values were exported to SPSS for the investigated frequency and time ranges. In a first step, data was analyzed according to the time and frequency windows reported previously (see 100 ms step analysis reported in Supplementary Table 3 of Schreiner et al., 2015). Secondly, post hoc explorative analyses were conducted according to visual inspection of the time-frequency plots (see Fig. 2) and the fact that it had been reported that especially fast spindle frequency increases with aging (Nicolas et al., 2001) in a predefined range according to work done by Mander et al. (2017, 2014).

2.8. Statistical analysis

The data was analyzed using analyses of variance with the between subjects factor age group (young vs. old adults) and the within subjects factor cue (cued vs. uncued). Due to local effects in Lehmann et al. (2016) and topographical accentuations in Schreiner et al. (2015) we also included the within-subjects factors hemisphere (left vs right) and topography (frontal vs central vs parietal). For follow-up analyses, paired-samples t-tests within the age groups or t-tests for independent samples were used. Values were adapted when equal variances could not be assumed. The level of significance was set to p = .05 (uncorrected).

3. Results

3.1. Behavioral data

In contrast to our previous findings in younger adults (Schreiner et al., 2015; Schreiner and Rasch, 2015), presentation of single Dutch words during sleep did not improve retrieval performance of the German translation in older adults: Participants remembered 73.93 ± 4.57% (*SEM*) words that were replayed during sleep ("cued" words) and 72.52 ± 4.56% uncued words, with memory performance before sleep set to 100%. Memory for cued and uncued words did not significantly differ (p > .70, d_z = 0.08) (see Fig. 1B). In contrast, younger adults remembered significantly more cued (98.27 ± 1.94%) than uncued words (89.82 ± 1.93%), $t(26)$ = 4.14, $p \leq .001$, d_z = 0.80). The interaction between cue and age group reached a statistical trend when testing two-sided, and was significant considering the expected direction of lower performance in older adults ($F(1,48)$ = 2.94, p = .09 (two-tailed); p = .046 (one-tailed), eta^2 = 0.06; f = 0.25). Generally, words cued during sleep were recalled better than uncued words (86.10 ± 2.35% vs. 81.17 ± 2.35%; main effect cueing $F(1,48)$ = 5.78; p = .02, eta^2 = 0.11) and retrieval success after sleep was lower in older adults (73.22 ± 3.11%, absolute number of words recalled 28.13 ± 2.61, range 3–51) as compared to our previous results in younger participants (94.05 ± 2.87%, main effect age group: $F(1,48)$ = 24.27, p < .001, eta^2 = 0.34, absolute number of words recalled 57.89 ± 3.26, range 25–103). Learning performance before sleep was generally better in older adults (61.02 ± 3.49%; range: 23.33–86.67%; absolute number of words 36.78 ± 2.06, range 14–52) than in younger adults (51.60 ± 2.69%; range: 22.50–70.83%, absolute number of words 61.89 ± 3.23, range 27–104, $t(48)$ = 2.26, p = .003, d = 0.64), probably because the learning task encompassed only 60 word-pairs in older adults as compared to a total of 120 word-pairs in younger participants. Presleep learning performance did not correlate with the success of cueing during sleep, neither in older adults ($r(22)$ = 0.16, $p \geq .40$) nor in younger adults ($r(26)$ = -0.23, $p \leq .20$, entire sample $r(49)$ = -0.64; p < .60).

In spite of the lack of an effect in older participants, the variability of cueing benefits on memory was remarkable (see Fig. 1B: variability of the data points between older and younger adults): while some participants profited from cueing during sleep with up to 33% of memory improvement, others showed an impaired performance induced by cueing of -42%. We further explored possible systematic differences between older adults that profited from cueing and others that did not, we split our sample into one group of "improvers" (n = 11) and one group of "decliners" (n = 8) defined by cueing benefits above or

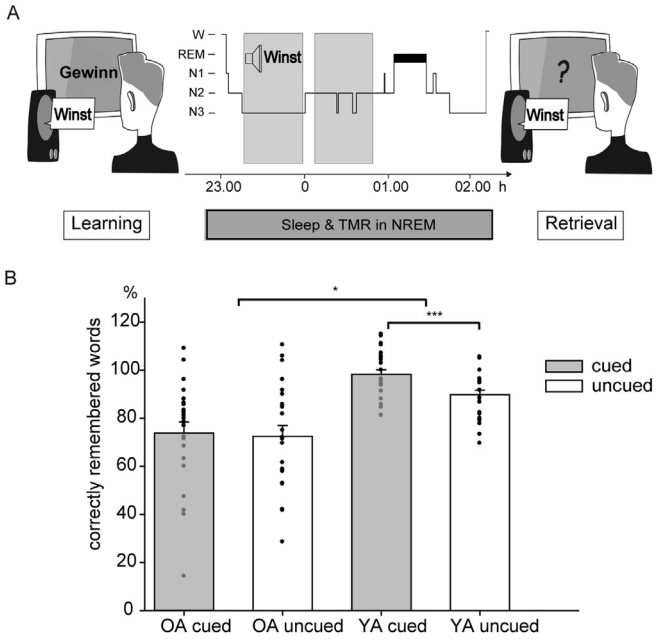

Fig. 1. Experimental procedure and behavioral results. (A) The experimental procedure (reproduced from Schreiner and Rasch, 2015) and (B) the behavioral results in older and younger adults displayed as means and single data points. Older subjects learned 60 Dutch-German word pairs before sleeping. During the retention interval, 50% of the correctly recalled and 50% of the not or incorrectly remembered words were replayed during NREM sleep (TMR). After 90 min of reactivation, participants were tested on their memory for the word pairs in a cued recall design. Results showed that subjects did not generally benefit from TMR (left panel) as was previously shown in younger adults (right panel). This lead to a significant interaction between age group (old vs. young) and cueing (cued vs. uncued words: p = .046 (one-tailed)). The single data points demonstrate the pronounced interindividual variability in the older age group. Asterisks indicate level of significance *p < .05; ***p < .001.

Table 1
Sleep stages during cueing in older and younger adults.

Sleep stage	Older adults (n = 23) *M* ± *SEM*	Younger adults (n = 27) *M* ± *SEM*	*p*
% Wake	13.47 ± 1.56	1.25 ± 0.35	< 0.001*
% N1	6.14 ± 0.71	5.07 ± 0.63	0.26
% N2	51.75 ± 3.37	50.68 ± 1.34	0.76
% N3	23.11 ± 3.77	31.20 ± 1.50	0.04
% NREM	74.86 ± 1.90	81.88 ± 1.19	0.002*
% REM	5.47 ± 1.10	11.32 ± 0.91	< 0.001*
Sleep latency (min)	12.46 ± 2.91	13.15 ± 2.09	0.85
Total min	287.52 ± 15.09	196.46 ± 3.23	< 0.001*
Sleep efficiency	0.83 ± 0.02	0.92 ± 0.01	< 0.001*
Wake (min)	40.35 ± 5.71	2.48 ± 0.69	< 0.001*
N1 (min)	17.04 ± 1.77	10.30 ± 1.44	0.004
N2 (min)	149.74 ± 13.10	99.65 ± 3.09	< 0.001*
N3 (min)	63.91 ± 9.54	60.65 ± 2.57	0.73
NREM (min)	213.65 ± 11.16	160.30 ± 2.29	< 0.001*
REM (min)	16.30 ± 3.12	22.41 ± 1.84	0.09

Note. Sleep stages in % and minutes ± standard errors of the mean (SEM) separately for older and younger adults of the sleep period during cueing. P-values indicate group comparisons. Bonferroni-corrected level of significance is $p = .003$. Asterisks indicate significant comparisons. Sleep efficiency was calculated as minutes in N1, N2, N3 and REM divided by the sum of total minutes asleep and sleep latency.

losses below 5%. As this analysis was however based on a very small subgroup we present the results in the Supplementary information.

3.2. Sleep data

Age group comparisons of the first night half in the experimental night (where cueing happened) showed that older adults had higher amounts of wake periods after sleep onset, but less % NREM sleep and REM sleep than younger adults did (all $p \leq .01$, see Table 1). Also sleep efficiency was reduced compared to the younger sample ($p < .001$). Older adults had longer total sleep times ($p < .001$) as it took on average longer to achieve the 90 min cueing in NREM sleep than in younger adults.

We found no significant correlation of the cueing benefit on memory with any sleep stage of the sleep period during cueing when analyzing the age groups separately (all $p > .10$). Taken both samples together, we found that amount of wakefulness negatively correlated with cueing success $r(49) = -0.29$, $p = .04$, whereas sleep efficiency correlated positively $r(49) = 0.28$, $p = .05$ (values not corrected for multiple comparisons) (Result of separate analysis: Young adults $r(26) = 0.05$, $p = .80$ and $r(26) = 0.01$, $p = .96$, Older adults $r(22) = -0.22$, $p = .32$ and $r(22) = 0.26$, $p = .24$ for wake and sleep efficiency,). Other sleep stages were again $p > .10$.

3.3. Wavelet analysis

To analyze the oscillatory response to cues during sleep in older adults we explored the difference between successful and unsuccessful cueing (gains vs. losses) in the time-frequency space using a wavelet range of 5 cycles and time window slides from -1–4 s in steps of 10 ms. In a first step, we restricted our analysis to frequency bands and time intervals previously reported for younger adults (see Fig. 3A and B): For theta activity (~ 6 Hz), we used an early time window (400–900 ms) and a late time window (1800–2500 ms). For spindle activity (~ 13 Hz) we used a time window between 400 and 1500 ms (see Schreiner et al., 2015, for details). As effects in younger adults had been particularly reported in frontal regions (Lehmann et al., 2016) and topographically fine-grained analyses were recommended (Mander et al., 2017), electrodes were grouped in six topographical regions (frontal/central/parietal × left/right, see Supplementary Fig. 2) and included as within-subject factors in an ANOVA as done previously (see Cordi et al., 2014 for details).

Analyzing early oscillatory power changes in the theta band between gained and lost words in older versus younger adults resulted in a trend in the age group main effect ($F(1, 33) = 3.90$), $p = .057$, $\text{eta}^2 = .11$). It indicated that power difference between gained versus lost words in older adults tended to be lower (0.05 ± 0.07) than in younger adults (0.23 ± 0.06; see Figs. 2 and 3A). This was further qualified by a significant hemisphere * age group interaction ($F(1, 33) = 5.76$, $p = .02$, $\text{eta}^2 = .15$). While power changes (i.e., gains > losses) in electrodes in the right hemisphere did not differ between age groups ($p > .20$), particularly the left-sided power increase for gains vs. losses in younger adults was significantly higher (0.30 ± 0.08%) than in older adults (0.04 ± 0.05%; $t(33) = 2.48$, $p = .018$, $d = 0.86$). Apart from a topography * hemisphere interaction ($F(2, 66) = 4.08$, $p = .03$, $\text{eta}^2 = .11$) all other comparisons were non-significant (all $p > .80$).

In separate analyses for old and young participants, older adults did not show any significant increase in theta activity in the early time interval after the reactivation cue (400–900 ms), for gains versus losses (all $p > .30$). In contrast, early theta power in younger adults significantly increased after gains vs. losses ($F(1, 19) = 11.93$, $p = .003$, $\text{eta}^2 = 0.39$). This was more pronounced on the left hemisphere (0.44 ± 0.08% vs. 0.14 ± 0.04%, $t(19) = 3.73$; $p \leq .001$, $d = 0.69$) as compared to the right side (0.38 ± 0.07 vs 0.22 ± 0.06, $t(19) = 2.65$, $p = .02$, $d = 0.56$) and resulted in an interaction between hemisphere and gains vs. losses in young participants ($F(1, 19) = 8.03$, $p = .01$, $\text{eta}^2 = .30$). Additionally, a three-way interaction between topography * hemisphere * cue was significant ($F(2, 38) = 5.82$, $p \leq .01$, $\text{eta}^2 = 0.23$), indicating that the effect was largest in left frontal brain areas as reported previously (see Schreiner et al., 2015).

In contrast to the reported age-dependent differences in the early time window, theta oscillations for gains vs. losses similarly increased in both older and young participants in the late time window (1800–2500 ms). Thus, no main effect of age was observed in this analysis ($p \geq .90$; see Fig. 3B). Both age groups showed a gain-related power change of about 10% (0.11 ± 0.05 and 0.11 ± 0.06 in younger and older adults, respectively, see Figs. 2 and 3B). This resulted in a significant main effect of gains vs. losses in older adults ($F(1, 14) = 6.70$, $p = .021$, $\text{eta}^2 = 0.32$), particularly between 1900 ms and 2500 ms after cue onset (see Supplementary Table 1 for a 100 ms step comparisons and black bars in Fig. 2B). In young adults, this main effect reached a statistical trend ($p = .06$). In younger participants, all single 100 ms steps between 1800 and 2500 ms were significant (all $p < .01$, see black bars in Fig. 2A and Supplementary information of Schreiner et al., 2015). All other main effects and interactions in the ANOVA were $p \geq .30$.

Based on the recent paper by Cairney et al. (2018) we tested spindle power also in the time window they found and which nicely corresponded to the late theta window (1.7–2.3 s after cueing). In older adults, none of the main effects or interactions was significant (all $p > .10$).

With respect to increases in spindle power previously observed in younger participants (~ 13 Hz, time window between 400 and 1500 ms), we observed a highly significant three-way interaction between topography * hemisphere * age group ($F(2, 66) = 5.80$, $p = .005$, $\text{eta}^2 = .15$), while the overall age group difference was non-significant ($p > .60$). Also, the topography * age group interaction was significant ($F(2, 66) = 10.49$, $p \leq .001$, $\text{eta}^2 = .24$). Follow-up tests in frontal electrodes revealed a significant age group effect ($F(1, 33) = 5.44$, $p = .026$, $\text{eta}^2 = .14$) which showed that young adults had more power increases for gains vs. losses (0.40 ± 0.63%) than older adults (0.06 ± 0.50%, see Fig. 3C). The age groups did neither differ in central ($p \geq .40$) nor parietal electrodes ($p = .15$), indicating a frontal maximum of the effect. In separate analyses, the interaction between topography and gains vs. losses reached only a trend in older adults ($F(2, 28) = 3.15$, $p = .06$, $\text{eta}^2 = .18$). Descriptively, the strongest

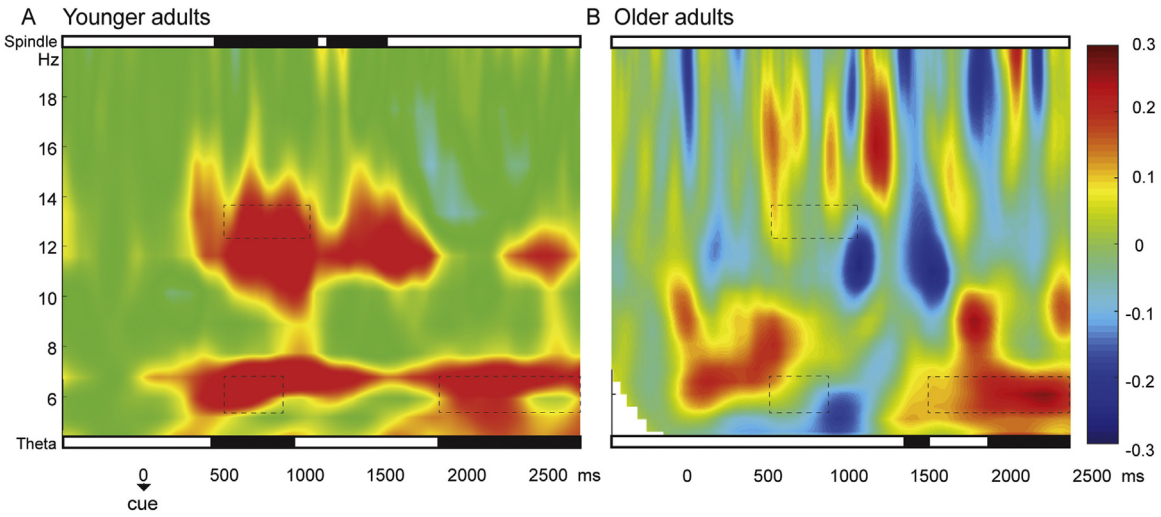

Fig. 2. Time-frequency analysis separately for younger and older adults. Time-frequency analyses in younger (A) and older adults (B) separately for the three investigated areas (indicated by black squares) on gained versus lost words. As example electrode we display F3 here. Time point 0 indicates cue presentation. The black bars on top (for spindles) and bottom (for theta) represent the 100 ms steps in which gain versus loss was significant ($p < .05$).

increases for gains vs. losses were observed at central electrodes, although no follow-up comparisons reached significance (all $p \geq .10$). No other main effect of interaction of this ANOVA was significant in older adults (all $p \geq .10$; see Fig. 3C and Supplementary Table 2 for 100 ms step comparisons). In younger adults, there was a stable frontal distribution of the spindle power increase for gains vs. losses ($t(19) = 2.92$, $p = .009$, $d = 0.53$ in frontal electrodes, no effect in central electrodes ($p \geq .90$) and a statistical trend in parietal electrodes ($p = .07$)), topography * cue interaction: $F(2, 38) = 14.06$, $p \leq .001$, $eta^2 = .43$). In addition, the interaction between hemisphere and gains vs. losses was significant ($F(1, 19) = 9.73$, $p = .006$, $eta^2 = .34$). Follow-up *t*-tests showed that the power difference between gains and losses was only significant in left (0.41 ± 0.10% versus 0.21 ± 0.04%, $t(19) = 2.32$, $p = .03$, $d = 0.44$), but not right-sided electrodes (0.31 ± 0.09% versus 0.35 ± 0.07%, $p \geq .70$). Also in young participants we did not observe any main effect of gains vs. losses ($p \geq .30$).

Following studies that report spindle frequency increases across lifespan (Nicolas et al., 2001), we also explored higher spindle frequencies (i.e. 13.5–15 Hz, see Mander et al., 2017, 2014) in 100 ms steps. Also here we did not find any significant power differences after gained versus lost words (all $p > .10$). This was neither the case when focusing only on frontal recording sites (all 100 ms steps $p > .10$; 400–1500 ms $p = .42$).

4. Discussion

Here we demonstrate that targeted memory reactivations (TMR) during sleep do not generally increase memory performance in older adults as compared to the memory-benefit of TMR observed in young participants (Schreiner et al., 2015). In older participants, retrieval performance for words that were not reactivated during sleep did not differ from memory for those words that we represented during NREM sleep. Also on the oscillatory level, the characteristic increases in theta and spindle power during an early time window (0.5–1.5 s) reported in young adults were absent in older adults. Only at later time windows (> 1.5 s), older adults generally also had increases in theta power associated with successful cueing during NREM sleep.

Several reasons could explain the lack of positive effects of TMR during NREM sleep in older adults. First, our results could indicate that the spontaneous memory reactivation mechanism occurring during NREM sleep in younger age is less functional in old age. This explanation is supported by findings from Gerrard et al. (2008), who show that although spontaneous reactivation during NREM of the activity pattern during sleep was preserved in aged rats, their temporal order of this reactivation was markedly impaired as compared to young rats. In addition, spatial memory score of the animals correlated with the degree of sequence reactivation in this study. In this case, one could assume that also targeting this mechanism by external memory cues during NREM sleep is less effective in older as compared to younger individuals, possibly explaining our null findings reported here. The notion of a less functional reactivation mechanism during NREM sleep in older age is consistent with studies reporting no or only small benefits of sleep on memory in older adults: For example, Scullin et al. (2017) recently reported no effects of an afternoon nap on memory performance in older adults (58–83 years). In contrast, younger adults showed the well-known sleep-benefits on memory. Similar results have been obtained by other groups (e.g., Cherdieu et al., 2014; Scullin et al., 2012; Wilson et al., 2012). Conversely, several studies have shown that sleep disruption or sleep deprivation results in fewer memory impairments in older as compared to young adults (Bonnet, 1989; Duffy et al., 2009; Nesthus et al., 1998). This was shown to be related to the disrupted timing between slow oscillations and sleep spindles in older compared to younger adults (Helfrich et al., 2018). These data suggest that the importance of sleep for memory is markedly reduced with age, possibly due to a reduction of an effective memory reactivation mechanism during NREM sleep.

Another possible explanation for the lack of TMR-induced memory benefits is the well-known reduction in SWS with age. Some authors have reported positive correlations between memory scores and the amount of SWS (Backhaus et al., 2007; Deak et al., 2011), possibly even mediated by the degree of prefrontal atrophy (Mander et al., 2014). However, others have reported also no or negative correlations between the amount of SWS and memory in old age (Mazzoni et al., 1999; Scullin, 2013). In the current study, percentage of SWS was also lower in older than younger adults. However, due to longer total sleep times in older adults, their total amount of SWS as scored by standard criteria was on average 64 min, whereas younger participants spent 61 min in slow-wave sleep. Thus, with respect to the total amount of slow-wave sleep, there should have been enough N3 sleep for benefits of TMR to occur. Thus, we consider it unlikely that the amount of SWS alone can explain the lack of TMR benefit on memory in our study and the reduced importance of sleep in general for memory in older age reported by others.

We also need to consider additional differences between the current TMR study and previous studies. For example, we adapted the learning

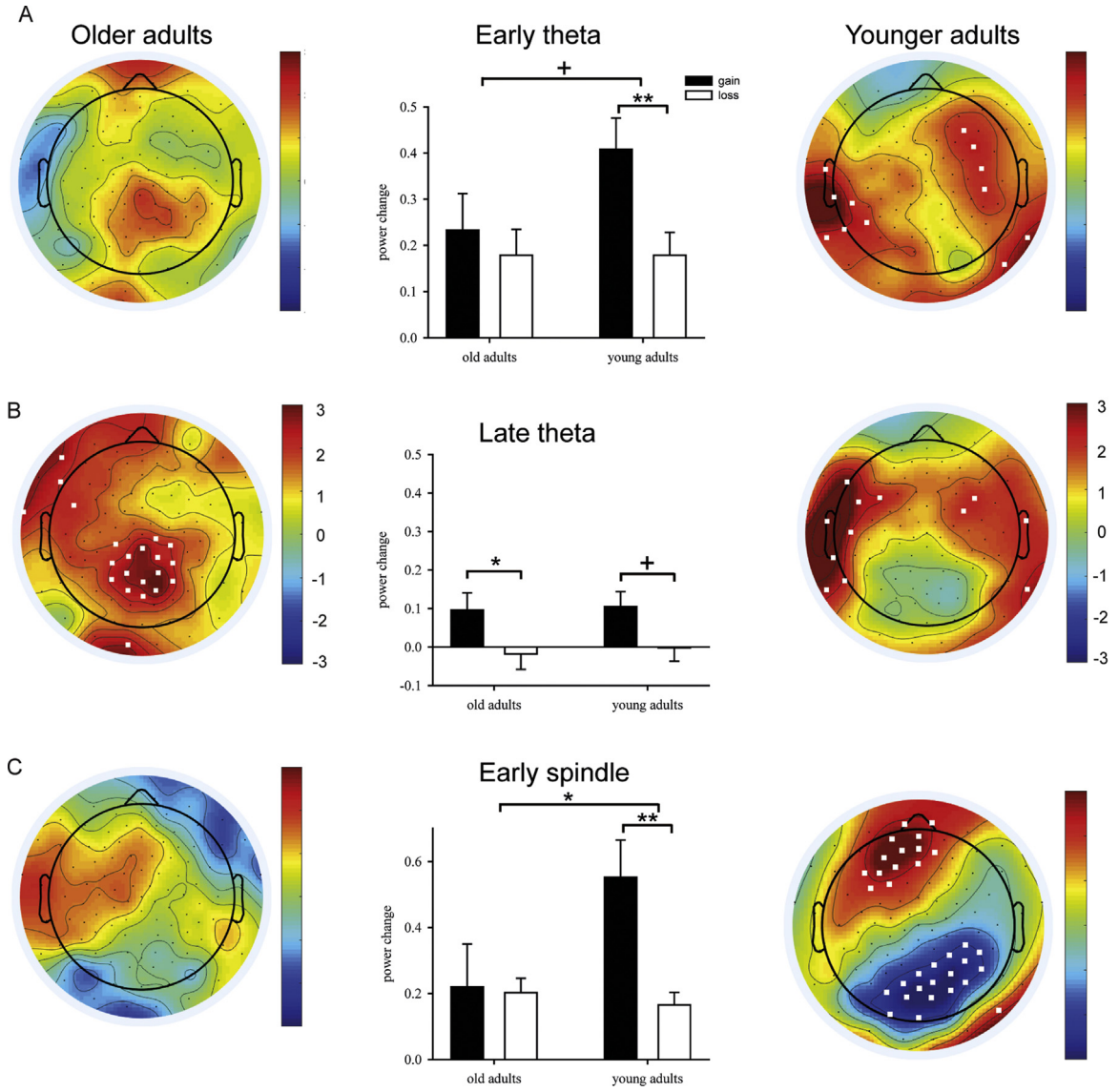

Fig. 3. Main results. Main oscillatory results for the three a prior defined analysis windows. A) In the Early theta window (5.6–6.6 Hz, 400–900 ms), older adults did not show any increase for successfully reactivated words (i.e., gained as compared to lost words, left panel) as previously observed in younger adults (right panel). The interaction including the average of all recording sites reached a statistical trend. B) For the late theta window (5.6–6.6 Hz, 1800–2500 ms), both old and young participants similarly exhibited increased theta oscillations at all recording sites for successfully reactivated words. (C) In contrast to younger adults, no increases in spindle oscillations (12.6–13.6 Hz, 400–1500 ms) during successful reactivation were observed in old adults at frontal recording sites (see main text, for significant main effects and interactions). Markers indicate significant results and statistical trends ($^{+}$: $p < .10$, *: $p < .05$, **: $p < .01$. A relative difference of 0.1 points corresponds to 10% change. The topoplots display *t*-values of gained versus lost words in older subjects (left panel) and younger adults (right panel). Significant electrodes are marked in white colour ($p < .05$, uncorrected).

task by reducing the amount of learning stimuli (i.e., from 120 to 60 word-pairs) and by increasing the number of repetitions (i.e., from 2 to 3 learning rounds). Some studies indicate that the number of stimuli (Feld and Born, 2017) and learning ability (Tucker and Fishbein, 2008) can influence the effect of sleep on memory. In addition, Creery et al. (2015) showed that targeted memory reactivation does not further strengthen memories for items learned almost perfectly. However, the immediate learning performance in the current study was at 60%, which is considered an optimal immediate performance level for obtaining sleep-benefits on memory (Diekelmann et al., 2009; Drosopoulos et al., 2007). Also a recent study showed that effects of TMR on forgetting processes during sleep did not differ between medium vs. high encoding strength (i.e., 50% vs. 75% remembered words at baseline before sleep), (Simon et al., 2018). Still, it might be possible that age-related differences in learning capabilities and encoding strategies might be the reason for the lack of sleep and TMR-induced memory benefits (Shing et al., 2008).

While in younger adults, all subjects had experienced gains and losses, 7 older adults did not show gains, one did not show losses and were thus excluded from the EEG analyses. The resulting 15 subjects did not show the gain-related power increases in early spindle and theta power observed in younger adults. However, gain-related changes in late theta power were more pronounced compared to loss related effects on theta power. As literature reports age-related spindle frequency increases, we additionally explored spindle power changes in higher frequencies after the cue. Also here, no relevant gain-related power changes appeared. According to our working-model (Schreiner and Rasch, 2017), increases in theta power after a memory cue during NREM sleep indicate successful reinstatement of the associated memory trace. Additionally, our recent work (Schreiner et al., 2018) showed that cue-induced reactivation patterns re-emerged at a 1 Hz rate. This finding indicates that reactivations might be coordinated by slow

oscillations and that cues trigger a repeated cycling of reactivation patterns (see also Bendor and Wilson, 2012; Rothschild et al., 2017). However, successful reinstatement alone is not sufficient to achieve memory benefits by TMR. In addition, increases in spindle activity are necessary to allow a successful stabilization and integration of the reinstated memory trace. According to this model, the early reinstatement of the memory trace observed in younger participants (0.5–1.5 s) is absent in older adults, possibly reflecting the impaired functionality of the reactivation mechanism in older age. Considering the expected cycling reactivation pattern one could speculate that the lacking early theta response indicates that TMR cues in older adults possess a minor capacity to initiate the reactivation processes properly. Thus, plastic processes associated with early spindle power increases might also not be capable of stabilizing the memory trace, as it was not yet successfully reinstated. Also in younger adults, a recent study shows that later spindle responses between 1.7 and 2.3 s might be even more critical for successful consolidation processes after reactivation during sleep, as they can contain category-specific memory information (Cairney et al., 2018). Possibly, the late theta responses in the older participants indicates that the successful reinstatement is only achieved in a later period (> 1.5 s). Then, however, still no parallel or consecutive spindle increase takes place, which might be related to the missing benefit by TMR during sleep in older adults. This could hint at an imbalance of the fine-grained interplay of oscillatory activity during sleep, which is crucial for the reactivation and stabilization of memories. However, this is highly speculative and requires further experimental confirmation in larger samples.

4.1. Limitations

As the lowest presleep learning level was at almost 25% we do not assume to have cognitively impaired subjects in the sample. However, we did not explicitly screen for MCI/dementia or other cognitive restrictions before inclusion of the participants. Moreover, the comparability between methods in the group of older and younger adults must further be discussed. Not only did younger adults learn double the amount of vocabularies as older adults did (120 versus 60), but also the type of cueing during sleep differed. While older adults were presented with only the Dutch words, younger adults were additionally confronted with Dutch-German word pairs during sleep ("cue + feedback" condition). Consequently, younger adults also received more (i.e. n = 80) different cues during sleep than older adults (i.e. n = 30). Due to the lower number of different cues, the number of repetitions of each word presented during sleep was almost doubled in older participants (ca. 34 repetitions) as compared to younger participants (ca. 17 repetitions). In addition, total sleep time differed between both groups. Both groups however received cues during a period of approximate 90 min of NREM sleep which was assumed the critical sleep stage for those effects. Moreover, a subgroup analysis with same sleep durations showed that behavioral effects of cueing still persisted in young, but not older adults. Thus, all these differences might have contributed to the different results reported for the two age groups. Note however, that all methodological changes we made to the learning and reactivation paradigm should have increased the chance to observe memory benefits of TMR during sleep in elderly participants. Further, we think that these task differences are considerably small: for example, when considering only the single cued words in younger adults, 40 of 80 learned words were presented again during sleep. This is in a similar range as in the current sample (30 out of 60 words). In addition, the cue + feedback condition in young participants did not produce any memory benefits and did not disturb the improving effects of single cues presented during the same time period of sleep (see Schreiner et al., 2015). Furthermore, note that differences in encoding ability between old and young participants are an inherent problem when examining age effects on memory consolidation. One strategy to reach similar encoding levels and to avoid possible ceiling effects in young or floor effects in older adults is to adapt task difficulty in an age-dependent manner. We chose this strategy to obtain a medium task difficulty in both age groups known to be optimal for sleep-associated memory consolidation processes (Diekelmann et al., 2009; Rasch and Born, 2013). Finally, with respect to the number of repetitions presented during sleep, one might even expect that older participants should have an advantage for TMR benefits during sleep. Thus, we do not think that the differences in task design can explain the entire effect pattern. Instead, we believe that the lack of TMR benefit on memory consolidation during sleep is truly age-dependent. However, replications of our null finding using exactly the same task design and reactivation procedure in young and old participants are necessary to provide additional evidence for our notion.

In sum, our results demonstrate that external reactivation of recently learned memory content does not generally help to improve memory in older adults. These findings indicate that the mechanism underlying sleep's support for memory consolidation changes across age. Still, when taking into account the high variability in memory benefits after TMR in older participants, it might be possible that reactivation and consolidation processes during sleep might have been persevered in at least some older individuals. Future studies are needed to identify possible mechanisms and biomarkers for maintaining sleep's role for memory also in old age.

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Conflict of interest

None.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2018.08.021.

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