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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

☆ We have given access to a prior version of this manuscript to the preprint platform https://www.biorxiv.org/. Data was not further disseminated in any other way.

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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