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Degree Project

The Impact of Targeted Memory Reactivation on Declarative Memory During Slow-Wave Sleep: A Systematic Review

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Abstract

The method targeted memory reactivation (TMR) uses specific stimulation when subjects are completing tasks and during sleep. The TMR process is known to influence the consolidation of declarative memories. The aim of this thesis is to conduct a systematic review on the effects of TMR on declarative memory consolidation during slow-wave sleep (SWS). The research question is to answer what effect TMR during SWS has on the consolidation of declarative memory in healthy humans when presented with associated cues of the targeted learning experiences. Eighteen studies were included in this review. Four studies found a significant effect of TMR on declarative memory consolidation, and 10 found a non-significant effect. In four studies the effect of TMR depended on different inclusions, analyses, and factors, for example between slow oscillation up-and down-states and between participants that vary in pre-sleep performance in the examined task. In contrast to previous findings, this review does not provide evidence for the effect of TMR on declarative memories during SWS. More research analysing different factors, such as different cues, age of participants, duration of SWS, and specific experimental tasks, needs to be done in the fields of TMR and auditory cues.

Keywords: targeted memory reactivation, TMR, sleep, slow-wave sleep, SWS.

The Impact of Targeted Memory Reactivation on Declarative Memory During Slow-Wave Sleep: A Systematic Review

While the conscious mind is resting when we sleep, the brain remains active (Lewis & Bendor, 2019). Neural networks in the brain are spontaneously reactivated when sleeping or resting due to being active during earlier encoding, and during this reactivation, memory consolidation occurs (Schouten et al., 2017; Tamminen et al., 2017). This systematic review focuses on targeted memory reactivation (TMR) and its role in declarative memory consolidation; the process in which newly made declarative memories transfer to neocortical neural networks. TMR has been demonstrated to enhance the consolidation of specific memories during sleep with the help of external stimulation, for instance, auditory cues. The results depend on the specific memory, sensory stimulation, and sleep stage examined (Cellini & Capuozzo, 2018; Pereira et al., 2022). The known effects of TMR on declarative memory are less forgetting, better memory recall, and memory generalization (Schouten et al., 2017). However, less is known about the specific effects of TMR, auditory cues, and the role of slow-wave sleep (SWS) on declarative memory consolidation (Ackermann & Rasch, 2014; Wilhelm et al., 2020).

Memory Consolidation and its Neural Basis

Memory consolidation is an ongoing process (Muehlroth et al., 2020; Tamminen et al., 2017) defined as “the process through which a memory trace is stabilized and integrated into a network of pre-existing related memories" (Schouten et al., 2017, p. 124). Consolidation leads additionally to the slow strengthening of memories (Muehlroth et al., 2020; Tamminen et al., 2017). Preliminary evidence of memory consolidation came from research observations in rodents, which showed a similarity between neurons firing during their activity during wakefulness and subsequent sleep. Likewise, neural activity representing new learned behavioural episodes during memory reactivation has been shown in rodents. Research in rodents has mainly focused on the effects in hippocampus during memory replay, evidence for neural reactivation, and research concerning human sleep (Lewis & Bendor, 2019). Reactivation and reallocation of mnemonic contents are critical mechanisms for memory consolidation to take place (Muehlroth et al., 2020).

Memory consolidation is divided into cellular/synaptic consolidation and brain systems consolidation. The cellular/synaptic consolidation is the immediate stabilization of new memories and occurs in the first hours after initiation (Dudai et al., 2015; Muehlroth et al., 2020). Also concerned is the transformation of new memories into long-term memories after encoding. Long-term memory is stored in cellular and synaptic nodes existing in the neural circuit. The brain systems consolidation involves the time-dependent reorganization of long-term memory in brain circuits after encoding (Bar et al., 2020; Dudai et al., 2015; Marshall et al., 2020; Stickgold, 2005). Evidence of memory consolidation is shown in hippocampal neurons which are active both during time awake and the following sleep (Lewis & Bendor, 2019).

Various brain regions are active during consolidation of different memories (Marshall et al., 2020). Consolidation of declarative memories is associated with activity in the hippocampus, ventral visual cortex, and fusiform gyrus. Consolidation of motor memories show activity in the rostral dorsal striatum which later is converted to the caudoventral part of the striatum (Marshall et al., 2020). Emotional memory consolidation is connected to the medial temporal lobe and amygdala (McIntyre et al., 2012).

Sleep Stages and Consolidation of Various Memories

Memory consolidation happens both when awake and asleep, nevertheless, consolidation is superior when asleep (Tamminen et al., 2017). The advantages when in the state of sleep can be explained by the absence of other sensory information (Creery et al., 2015). The most coherent feature of human sleep is the approximately 90-minute cycles of non-rapid eye movement sleep (NREM) and rapid-eye-movement (REM) sleep (Brown et al., 2012; Stickgold, 2005). During the early onset of sleep, NREM sleep progresses more into its deeper stages. The first REM sleep episode occurs 90 minutes into sleep and throughout the night its proportion increases and the depth of NREM sleep decreases (Brown et al., 2012).

During NREM sleep, a sequence of rhythmic neural activity occurs. NREM sleep is divided into three different stages which vary in depth (Moser et al., 2009; Stickgold, 2005). The first stage (N1; light sleep) normally takes up a small portion of time asleep, and is mostly thought of as a transition phase from wakefulness to sleep. N1 is characterized by a low voltage oscillatory activity in the range of 2-7 Hertz (Hz). The second stage in NREM sleep (N2; intermediate sleep) occurs during the whole night and is associated with sleep spindles that last for at least half a second and K-complexes (Ackermann & Rasch, 2014; Himanen & Hasan, 2000). K-complexes are "characterized by a short surface-positive wave followed by a larger surface-negative wave and then a positive wave" (Caporro et al., 2012, p.304). K-complexes are induced by multiple arousal stimulus and are often followed by a sleep spindle, additionally they are a marker of delta EEG activity in SWS (Caporro et al., 2012). Sleep spindles are occurrences of waxing and waning oscillatory activity in the range of 11-15 Hz and only occur during sleep. The N2 stage is associated with enhancement and consolidation of declarative memory (Ackermann & Rasch, 2014; Gennaro & Ferrara, 2003). The third stage of NREM sleep (N3) is the most profound and referred to as SWS. Characteristics of SWS are its high-amplitude oscillatory activity in the range of slow delta (Hz) and sleep spindles, as well as a rotation of depolarized up-states and hyperpolarized down-states activity (voltage transitions in the absence of sensory stimuli, important for working memory) (Ackermann & Rasch, 2014; Cox et al., 2014; Holcman & Tsodyks, 2006; Stickgold, 2005). More rapid rhythms are created that include beta/gamma band (20 Hz) activity which primarily occurs during the up state (Ackermann & Rasch, 2014; Cox et al., 2014; Stickgold, 2005). SWS mainly takes place in the first half of the night (Ackermann & Rasch, 2014). Observations throughout SWS display that prefrontal cortex cells fire 100 ms after cells in the hippocampus in this specific sleep stage, resulting in a possibility for synaptic plastic changes in neocortex cells. SWS is shown to have a crucial role in the transformation of declarative memories from the hippocampus to the neocortex and declarative memory consolidation (Ackermann & Rasch, 2014; Wierzynski et al., 2009).

Characteristics of REM sleep include rapid eye movements, a total loss of muscle tone (Brown et al., 2012), a mixed frequency oscillatory activity, more specifically a combination of low amplitude oscillations in the 11–15 Hz range, and hippocampal theta oscillations (Ackermann & Rasch, 2014). Procedural skills (motor skills), emotional memory (amygdala mediated cued fear conditioning), and object recognition (identifying objects), which are all independent of cortico-hippocampal circuitry, are memories believed to benefit from REM sleep (Dudai et al., 2015; Hellman & Abel, 2007). REM sleep happens after SWS and seems to help reorganize representations occurring during system consolidation (Dudai et al., 2015). Activity in limbic neurons during REM leads to the suggestion that this stage plays a part in the processing of emotional memories (for instance fear memory) (Brown et al., 2012; Nyberg et al., 1998).

Targeted Memory Reactivation

The term TMR was recently put forward, although research on the subject goes back as far as 1950. TMR is a technique applying sensory stimuli during sleep to manipulate the consolidation of specific memory (Hu et al., 2020). When conducting a TMR study, sensory cues and target information are associated with each other during a learning period while awake. Later, when subjects are asleep, the cue alone is presented during SWS to reactivate the target information (Cellini & Capuozzo, 2018; Hu et al., 2020; Lewis & Bendor, 2019). After sleep and presentation of cues, storage of the targeted memory is stronger during reactivation, which in turn leads to a better recall of that specific memory (Hu et al., 2020). Memory performance related to a cue presentation is in 40 minutes enhanced to the same level as a 90-minute sleep without an external reactivation (Schouten et al., 2017).

Different types of cues are used in TMR studies, for example, auditory or olfactory cues. Olfactory cues are often preferred because participant rarely wake up during the presentation of the cue (Bar et al., 2020).

Depending on the study, TMR either leads to an increase or decrease in the consolidation of information when asleep (Cellini & Capuozzo, 2018; Schouten et al., 2017). For example, Simon et al. (2018) studied memory loss after TMR. To successfully decrease memory participants were taught to associate the act of forgetting with a forget-tone. Later the forget-tone stimuli were presented together with another sound stimuli associated with the task during sleep. Participants showed less recall and more impaired memory of reactivated than non-reactivated stimuli (Simon et al., 2018). When a cue is presented to the subject, it usually causes retrieval of more than one memory which leads these memories to compete about being strengthened or weakened. It has been shown that when memories are only moderately activated (not enough to win the competition against other memories), they become weaker (Antony et al., 2018), which is displayed in the study by Simon et al. (2018).

TMR is based on the activation of hippocampal neuronal networks and their encoding of new information during sleep. Activation during cued-induced memory consolidation during sleep is specifically shown in the left hippocampus, right parahippocampal cortex, retrosplenial cortex, temporal cortex, and medial frontal areas (Schouten et al., 2017).

The Present Thesis

The aim of this thesis is to conduct a systematic review on the effects of TMR on declarative memory consolidation during SWS. The research question is to answer what impact TMR during SWS has on the consolidation of declarative memory in healthy humans when presented with associated cues of the targeted learning experiences. Research on TMR and declarative memory is important because it can lead to further knowledge regarding the neural mechanisms underlying the consolidation and transformation of memories. Furthermore, knowledge concerning how to impact memory consolidation may contribute to future learning processes (Hu et al., 2020; Witkowski et al., 2020).

Methods

Search Strategy

The literature search followed the PRISMA 2009 flow diagram (Moher et al., 2009). Electronic databases used in the literature search were Web of Science, Scopus, and Medline EBSCO. Different search strings were tested to get specific and relevant amounts of search results. Searches were performed by including all fields and with the following keywords and Boolean operators: ("targeted memory reactivation" OR TMR) AND ("slow-wave sleep" OR SWS). The presented final search was done on 6 April 2022 and resulted in a total of 548 articles (see Figure 1). Four additional articles of interest were found via other sources. During screening, duplicates were removed resulting in 462 articles. Three hundred and eighty-eight review articles, book chapters, and articles researching wrong topics were later excluded. Seventy-four articles were tested for eligibility in full text, resulting in the removal of 56 articles: and a total of 18 articles remaining.

Inclusion and Exclusion Criteria

Studies were included if they fulfilled the following criteria. Participants in the studies are human subjects over 18 years old and healthy; having no neurological, psychiatric, sleep, or motor disorders. Articles are peer-reviewed original research studies and in English.

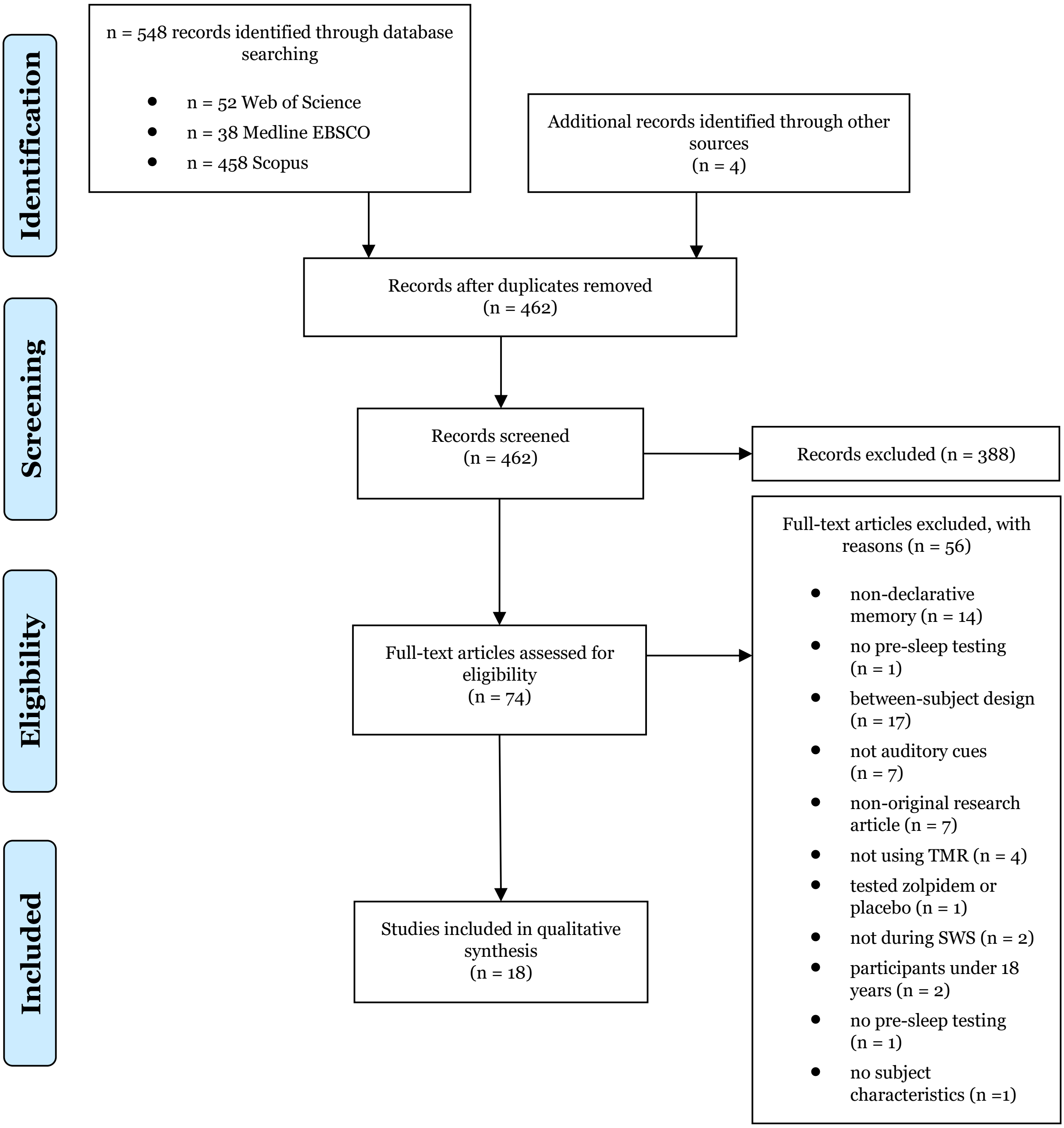
Articles report studies testing the effects of targeted memory reactivation on declarative memory via a learning experience both before and after sleep and the presentation of cues during SWS. Assessment tools used to detect the subject's sleep stages are electroencephalography (EEG) or polysomnography (PSG). Included articles have a within-subject study design and present cues in the auditory modality. The focus was on auditory cues to examine more in-depth on one of the most studied TMR cues.

Data Extraction

Data extracted from the articles include (1) references, (2) sample size, (3) female ratio, (4) age, (5) country, (6) sleep length, (7) memory task, and (8) results. Shown results are participant's results on the memory task before and after SWS.

Figure 1

PRISMA 2009 Flow Diagram



Note. Standard flow diagram used to document the literature search process (Moher et al., 2009)

Results

Study Characteristics

Table 1 displays the sample characteristics, experimental characteristics and results of the experiments included in the systematic review. Eleven of the studies were conducted in USA (Antony et al., 2018; Batterink et al., 2017; Creery et al., 2015; Henin et al., 2019; Sanders & Beeman, 2021; Sanders et al., 2019; Schechtman et al., 2021; Vargas et al., 2019; Wang et al., 2019; Whitmore et al., 2022; Witkowski et al., 2021), two in the UK (Cairney et al., 2016, 2017), three in Switzerland (Cordi et al., 2018; Groch et al., 2017; Göldi et al., 2019), one in The Netherlands (Van Dongen et al., 2012), and one in Germany (Wang et al., 2022). The sample size ranged from 12 to 58, adding up to a total of 493 participants. The subjects' mean age ranged from 19.87 to 71.00. All but three studies included both female and male subjects. Exceptions were Wang et al. (2022) and Cairney et al. (2017) which included only men, and Vargas et al. (2019) who gave no information about subjects' gender. The minimum mean sleep length (how long subjects slept during the experiment) in the included studies was 59 minutes, and maximum mean sleep was 8 h or a whole night. No information about how participants were woken up if needed are given. SWS was determined by electroencephalogram (EEG) in all included studies. All but six of the included studies used electromyogram (EMG) (Cairney et al., 2016, 2017; Groch et al., 2017; Sanders et al., 2019; Sanders & Beeman, 2021; Van Dongen et al., 2012). Electrooculogram (EOG) was used by every included study except eight (Cairney et al., 2016, 2017; Groch et al., 2017; Göldi et al., 2019; Henin et al. 2019; Sanders et al., 2019; Sanders & Beeman, 2021; Van Dongen et al., 2012). Additionally, two studies used Polysomnogram (PSG) (Cairney et al., 2016, 2017), one study used functional magnetic resonance imaging (fMRI) (Van Dongen et al., 2012), and two studies used electrocardiographic (ECG) (Cordi et al., 2018; Göldi et al., 2019).

Object-Location and Object-Word Tasks

Seven articles used an object-location task, and two articles used an object-word task to measure the effect of TMR. Antony et al. (2018) analysed spatial forgetting and change in memory during a learning experience where participants were associated pictures of 24 celebrities and 24 landmarks with 48 sound cues. Half of the cues were presented during SWS. A significant difference between the forgetting of cued stimuli (M = 1.6 ± 8.4) and uncued stimuli (M = 24.7 ± 10.9; p = 0.039) was found, were forgetting was significantly less frequent in the cued compared to the uncued stimulus (Antony et al., 2018).

Creery et al. (2015) associated 50 objects with a location. A sound was played when objects were shown, and participants were directed to move the object to its correct location. Error in pre-sleep recall in the cued condition (M = 83.7 ± 4.2) and the uncued condition (M = 84.2 ± 5.1) showed no significant difference (p = 0.80). Mean error in post-sleep recall was 89.5 (± 6.4) in the cued condition and 95.0 (± 5.7) in the uncued condition.

Table 1

Characteristics and Results of Articles Included in the Systematic Review

References	Sample size (f)	Age (years)	Country	Sleep length	Assessment tool	Memory task	Results
Antony et al. (2018).	18 (10)	(M = 21.8) (range = 18-33)	USA	90 min	EEG & EMG & EOG	object-location	forgetting pre/post-sleep: cued (M = 1.6 ± 8.4), uncued (M = 24.7 ± 10.9), (p = 0.039)
Batterink et al. (2017).	26 (14)	(M = 20.7) (SD = 1.28)	USA	90 min	EEG & EMG & EOG	word-pair	recall accuracy post-sleep: cued (M = 79.2%, SD = 16.1%), uncued (M = 79.9%, SD = 13.3%), (p > 0.41)
Cairney et al. (2016).	30 (16)	(M = 19.87) (SD = 1.94) (range = 18-27)	UK	90 min	EEG & PSG	object-word & object-location	object-location recall (cm): pre-sleep: TMR (2.91 ± 0.16), no TMR (2.81 ± 0.15), post-sleep: TMR (3.19 ± 0.19), no TMR (3.35 ± 0.22), (p < 0.71) object-word recall (%): pre-sleep: TMR (75.47 ± 2.14), no TMR (75.33 ± 2.16), post-sleep: TMR (86.00 ± 1.77), no TMR (86.13 ± 1.68), (p = 1.0)
Cairney et al. (2017).	28 (0)	(M = 20.32) (SD = 1.54) (range = 18-24)	UK	8 h	EEG & PSG	word-location	Paired associations: sound-word recall: pre-sleep (79.85 +- 2.55), post-sleep (79-85 +- 2.44), sound-word forgetting: cued (2.24 +- 0.92), uncued (5.00 +- 1.23) speech-word recall: pre-sleep (81.89 +- 2.69), post-sleep (82.27 +- 2.45), speech-word forgetting: cued (1.23 +- 0.59), uncued (3.93 +- 1.20) recall (p = 0.53), forgetting (p = 0.014) locations: sound-word recall: pre-sleep (60.08 +- 4.65), post-sleep (59.57 +- 4.58), sound-word forgetting: cued (16.32 +- 5.13), uncued (19.42 +- 5.67) speech-word recall: pre-sleep (55.61 +- 4.49), post-sleep (55.10 +- 4.50), speech-word forgetting: cued (19.72 +- 4.86), uncued (18.47 +- 5.76) recall (p = 0.24), forgetting (p = 0.76)

Cordi et al. (2018).	23 (15)	(M = 71.00) (SD = 5.86) (range = 62-83)	Switzerland	minimum of 3h	EEG & ECG & EMG & EOG	word-pair	recall: cued (M = 73.9, SEM = 4.57%), uncued (M = 72.52, SEM = 4.56%) (p > .70)
Creery et al. (2015).	20 (12)	(range = 19-23)	USA	90 min	EEG & EMG & EOG	object-location	recall: test-1 error cued (83.7 ± 4.2), uncued (84.2 ± 5.1), (p = 0.80), test-2 error cued (89.5 ± 6.4), uncued (95.0 ± 5.7) forgetting: cued (5.8 ± 4.2), uncued (10.8 ± 4.3) cue benefit: (p = 0.41)
Groch et al. (2017).	16 (11)	(M = 20.25) (SEM = 1.95) (range = 18-25)	Switzerland	whole night	EEG	object-word	memory recall: cued-uncued (prior knowledge available) (p = 0.05), cued-uncued (no prior knowledge available) (p > 0.41)
Göldi et al. (2019).	22 (18)	(M = 20.85) (SD = 0.28)	Switzerland	3 h	EEG & EMG & ECG	word-pair	SO up-states: cued (M = 99.3 ± 2.89%), uncued (M = 90.92 ± 3.14%), (p = 0.019) SO down-states: cued (M = 96.83± 4.27%), uncued (M = 90.92 ± 3.14%), (p = 0.366)
Henin et al. (2019).	Experiment 1: 12 (6) Experiment 2: 19 (9)	Experiment 1: (M = 23.3) (SEM = 0.8) Experiment 2: (M = 23.3) (SEM = 0.9)	USA	Experiment 1: 2 h Experiment 2: whole night	EEG & EMG	word-pair	Experiment 1: word-pair retention: cued-uncued BF (0.302, error % 0.019), virtual reality speed improvement: cued-uncued BF (0.299, error % 0.019) Experiment 2: word-pair retention: cued-uncued BF (0.249, error % 0.012)
Sanders et al. (2019).	57 (38)	(M = 20.01) (SD = 1.92) (range = 18-29)	USA	whole night (M = 393 min per night)	EEG	puzzle-solving	solving: cued puzzles (M = 31.7% ± 28.3%), uncued puzzles (M = 20.5% ± 18.9%), (p = .002) main effect cueing (p = .003)
Sanders & Beeman (2021).	58 (46)	(M = 19.82) (SD = 1.62) (range = 18-26)	USA	whole night	EEG	puzzle-solving	solving: cued (M = 68.6% ± 26.9%), uncued (M = 70.4% ± 26.7%), (p = .680)

Schechtman et al. (2021).	31 (21)	(M = 20.81) (SD = 2.96) (range = 18-30)	USA	90 min	EEG & EMG & EOG	object-location	cuing main effect errors change (p = 0.52)
Van Dongen et al. (2012).	56 (42)	(range = 18-27)	The Netherlands	2 h	fMRI & EEG	object-location	pre-sleep error (cm): cued (M = 2.66 ± 0.12), uncued (M = 2.79 ± 0.13), (p = 0.13) pre- to post-sleep error (cm): cued (M = -0.44 ± 0.11), (p = 0.001), uncued (M = -0.33 ± 0.11), (p = 0.018)
Vargas et al. (2019).	24 (No Information)	(range = 18-24)	USA	90 min	EEG & EMG & EOG	object-location	pre-nap error in pixels: cued: A trials (M = 75.6 ± 2.6), uncued: A trials (M = 74.8 ± 2.3), post-nap error in pixels: cued: A trials (M = 79.2 ± 2.7), uncued: A trials (M = 80.3 ±3.0), forgetting score error in pixels: cued: A trials (M = 3.6 ± 1.2), uncued: A trials (M = 5.5 ± 1.6), cued-uncued error change (p < .05)
Wang et al. (2019).	24 (14)	(M = 22.3) (range = 18-33)	USA	90 min	EEG & EMG & EOG	object-location	pre-sleep: cued (M= 0.55 ± 0.024), uncued (M = 0.55 ± 0.027), (p 0.95) post-sleep: cued (M = 0.32 ± 0.02), uncued (M = 0.29 ± 0.02), (p = 0.17)
Wang et al. (2022).	16 (0)	(M = 24.4) (SD = 0.8) (range = 18-30)	Germany	8 h	EEG & EMG & EOG	word-pair	pre-sleep: up-state cued (M = 16.19 ± 0.44), uncued (M = 15.94 ± 0.47), down-state cued (M = 16.63 ± 0.57), uncued (M = 16.67 ± 0.55) post-sleep: up-state cued (M = 95.96% ± 2.82%), uncued (M = 95.53% ± 2.30%), down-state cued (M = 93.98% ± 2.39%), uncued (M = 96.50% ± 2.87%) cued-uncued (p = 0.70)
Whitmore et al. (2022).	24 (16)	(M = 23.38) (SD = 4.44) (range = 18-31)	USA	(M = 59 min) (range = 32-92 min)	EEG & EMG & EOG	face-name	post-sleep change: name recall: cued (M = 0.75 ± 2.03), uncued (M = 0.21 ± 1.70), (p = 0.36) face recognition: cued (M = 0.37 ± 0.50), uncued (M = 0.49 ± 0.54), (p = 0.22)
Witkowski et al. (2021).	29 (21)	(M = 21.07)	USA	90 min	EEG & EMG & EOG	sound-name	generalization performance accuracy: pre-sleep: (M = 57.85% ± 2.87%), cued-uncued (p = 0.47), post-sleep: cued-uncued (p = 0.93) specificity performance accuracy: pre-sleep: (M = 60.73 % ± 2.37%), cued-uncued (p = 0.59), post-sleep: cued-uncued (p = 0.02)

Note. f = females, SO = slow oscillations, BF = Bayes factor

The mean forgetting score (test-2 error - test-1 error) for all participants was 5.8 (± 4.2) in the cued condition and 10.8 (± 4.3) in the uncued condition, which does not demonstrate a significant benefit of cues (p = 0.41) (Creery et al., 2015).

Van Dongen et al. (2012) show objects on a computer screen at the same time as a sound was played and subjects were asked to place the object in its correct location. Pre-sleep test showed that the mean and standard deviation (SD) in cued error (M = 2.66 cm ± 0.12 cm) and uncued error (M = 2.79 cm ± 0.13 cm) did not significantly differ (p = 0.13). Both cued error in pre- to post-sleep performance (p = 0.001) and uncued error in pre- to post-sleep performance (p = 0.018) showed a significant decrease in error performance (Van Dongen et al., 2012). These results means that forgetting was decreased in both conditions, leading to a significant impact of TMR when cues were used. However, a significant decrease was shown without the usage of cues, meaning no significant differences between the cued and uncued conditions was found.

Another object-location task was used by Vargas et al. (2019) and Wang et al. (2019). Vargas et al. (2019) used images of 100 objects and Wang et al. (2019) used 128 objects. Both studies divided their number of objects into two equally big groups and associated each object in one of the groups with a specific sound (A objects). The other objects in the second group were paired to one object from the first group (B objects). Each pair, including one A object and one B object, were separately presented on a screen with the associated sound. Participants were asked to place A objects in their location with the help of the associated sound. With help of A objects, participants were asked if they remembered the paired B object and its screen location. Half of the sound cues were presented to subjects during SWS. Relevant results are of the A trials, where participants were directed to place A objects in their location with the help of a sound cue. Mean pre-sleep error of cued objects was 75.6 (± 2.6) and of uncued objects 74.8 (± 2.3). Mean post-sleep error of cued objects was 79.2 (± 2.7) and of uncued objects 80.3 (±3.0). Mean forgetting score of cued objects was 3.6 (± 1.2) and of uncued objects 5.5 (± 1.6). A significant difference between change in error of cued and uncued objects was shown, which displays a significant effect of TMR (p < .05) (Vargas et al., 2019).

Wang et al. (2019) used images of 128 objects associated with a location. Half (64) objects were associated with a sound. No significant difference between pre-sleep performance in cued (M = 0.55 ± 0.024) and uncued (M = 0.55 ± 0.027) conditions (p = 0.95) was found. Post-sleep performance in cued (M = 0.32 ± 0.02) and uncued (M = 0.29 ± 0.02) conditions showed simultaneously no significant differences (p = 0.17) (Wang et al., 2019).

Schechtman et al. (2021) used images of objects, object parts, or people as stimuli. Forty-five picture sets with the same theme were used, including 24 sets containing six main images and 12 lure images (multi-item sets) and 21 sets containing one main image and two lure images (one-item sets). The main images were used in a spatial-memory task and the lure images only in an item-recognition task. Eighteen one-item sets, 18 two-item sets, and 6 six-item sets were paired with a specific location on a screen, which participants later were tested on. No significant change in error between cued pre-and-post sleep results was found ($p = 0.52$), no significant effect of TMR (Schechtman et al., 2021).

Cairney et al. (2016) tested subjects in association of words and locations to pictures in both cued and uncued conditions. Fifty pictures of objects or scenes (semantically related to the used sounds) were each paired with one of 50 words. First, participants learned to pair pictures and words. Secondly, the objects were shown in a specific location on a screen together with the associated sound. The object-word pre-sleep test (cued %: $M = 75.47 \pm 2.14$, uncued %: $M = 75.33 \pm 2.16$) and the post-sleep test (cued %: $M = 86.00 \pm 1.77$, uncued %: $M = 86.13 \pm 1.68$) did not show a significant TMR effect ($p = 1.0$). The object-location pre-sleep test (cued %: $M = 2.91 \pm 0.16$, uncued %: $M = 2.81 \pm 0.15$) and the post-sleep test (cued %: $M = 3.19 \pm 0.19$, uncued %: 3.35 ± 0.22) showed no significant TMR effect ($p < 0.71$) (Cairney et al., 2016).

Groch et al. (2017) used an object-word association task. Pseudo-words and pictures of familiar (prior knowledge) and novel (non-prior knowledge) objects were associated by subjects in a learning session. Half of the words associated with familiar and novel objects were presented to subjects during SWS. The cue benefit relates to the existence of prior knowledge, and cued stimuli increased memory recall compared to uncued stimuli when taking prior knowledge into account ($p = 0.05$). Without prior knowledge, no benefit of cues was found ($p > 0.41$) (Groch et al., 2017).

Studies which used object-location and object-word tasks showed a significant effect of TMR in two out of the eight studies (Antony et al., 2018; Vargas et al., 2019). Groch et al. (2017) found a significant effect of TMR when tested knowledge was known by subjects before the experiment. Four studies found no significant effect of TMR (Cairney et al., 2016; Creery et al., 2015; Schechtman et al., 2021; Van Dongen et al., 2012). Van Dongen et al. (2012) showed a significant change between pre-and-post sleep recall in both cued and uncued conditions, but no significant difference between the conditions and therefore no significant effect of TMR.

Word-Location Task

One study used a word-location task to study the effect of TMR in recall and forgetting of speech-word pairs and sound-word pairs with an associated location (Cairney et al., 2017). Forgetting was measured between pre-sleep and post-sleep results. The stimuli used as the pair-associate targets were 70 words divided into two groups with 35 words each. Used as cues were 35 spoken words and 35 environmental sounds. Results were analysed in recall and forgetting of paired associations and location, where location recall in pre-sleep only includes the correctly recalled. The mean paired association recall in the sound-word condition was 79.85 (± 2.55) in pre-sleep and 79.85 (± 2.44) in post-sleep. The mean forgetting of sound-word was 2.24 (+- 0.92) in the cued condition and 5.00 (± 1.23) in the uncued condition. The mean recall of speech-word was 81.89 (± 2.69) in pre-sleep and 82.27 (± 2.45) in post-sleep. The mean forgetting of speech-word was 1.23 (± 0.59) in the cued condition and 3.93 (± 1.20) in the uncued condition. Recall of paired associates showed no significant effect of TMR ($p = 0.53$). A significant main effect of TMR was found in forgetting of recall ($p = 0.014$). The mean location recall in sound-word was 60.08 (± 4.65) in pre-sleep and 59.57 (± 4.58) in post-sleep. The mean forgetting of the location associated with sound-word cues was 60.08 (± 4.65) in pre-sleep and 59.57 (± 4.58) in post-sleep. The mean location recall speech-words were 55.61 (± 4.49) in pre-sleep and 55.10 (± 4.50) in post-sleep. The mean forgetting of speech-words was 19.72 (± 4.86) in the cued condition and 18.47 (± 5.76) in the uncued condition. No significant main effect of TMR was found in location recall ($p = 0.24$) or forgetting of location ($p = 0.76$) (Cairney et al., 2017).

Word-Pair Tasks

Five studies tested TMR using a word-pair task. Batterink et al. (2017) taught participants the meaning of 60 novel vocabulary words. Two different cues were used: “sound-cues” (environmental sounds) and “word-cues” (spoken auditory cues). The recall accuracy of words post-sleep between the cued condition (M = 79.2% ± 16.1%) and the uncued condition (M = 79.9% ± 13.3%) was not significantly different between the conditions ($p > 0.41$) (Batterink et al., 2017).

Cordi et al. (2018) and Göldi et al. (2019) tested participants in Dutch-German vocabulary pairs. One study used 60 vocabulary pairs (Cordi et al., 2018) and one study used 120 vocabulary pairs (Göldi et al., 2019). Subjects in the study by Cordi et al. (2018) were tested in two feedback and one final recall trial before sleep. Half of the correctly recalled words and half of the incorrectly recalled words were cued during sleep. Recall of cued words (M = 73.9, SEM = 4.57%) and uncued words (M = 72.52, SEM = 4.56%) showed no significant difference in memory performance ($p > 0.70$) (Cordi et al., 2018). Göldi et al. (2019) presented cues separately in slow oscillations (SO) up-states and down-states. Cues presented during SO up-states (M = 99.3 ± 2.89%) and the uncued condition (M = 90.92 ± 3.14%) showed a significant effect of TMR ($p = 0.019$). Cues presented during SO down-states (M = 96.83 ± 4.27%) and the same uncued condition showed no significant TMR effect ($p = 0.366$) (Göldi et al., 2019).

Henin et al. (2019) tested participants in two experiments with different in experiment 1 were instructed to a two-hour cued nap, while participants in experiment 2 were instructed to cued sleep overnight. Experiment 1 used 100 word-pairs and experiment 2 used 120 word-pairs which were to a certain extent semantically related to each other. Bayes factor (BF) was used to indicate whether evidence for the null hypothesis exist or not, a BF should be over 1 to be able to reject the null hypothesis. In experiment 1, word-pair retention of cued-uncued stimuli had a BF of 0.302 and an error of 0.019%, which showed no significant difference between cued and uncued stimuli on memory performance. A verbal associative task was also used in experiment 1 and measured if memory performance benefits from cues in the speed improvements through the used virtual reality (VR) environment. Between cued-uncued stimuli in VR speed improvement BF (0.299) and error (0.019%) showed no significance of TMR usage. In experiment 2, word retention between cued-uncued in BF (0.249) and error (0.012%) showed no significant difference.

Wang et al. (2022) used a task including two lists, each with 40 German words moderately semantically connected, which later were paired. Participants were tested for two nights separated by a mean of 14 days. During the first night, real-time cues were presented to the participants during SO up-states, and during the second night, cues were presented during SO down-states. EEG was used to measure SO up-and-down-states. Mean pre-sleep recall in SO up-state was 16.19 (± 0.44) in the cued condition and 15.94 (± 0.47) in the uncued condition. Mean pre-sleep recall in SO down-state was 16.63 (± 0.57) in the cued condition and 16.67 (± 0.55) in the uncued condition. Mean post-sleep recall in SO up-state was 95.96% (± 2.82%) in the cued condition and 95.53% (± 2.30%) in the uncued condition. Mean post-sleep recall in SO down-state was 93.98% (± 2.39%) in the cued condition and 96.50% (± 2.87%) in the uncued condition. Post-sleep main effect between cued and uncued word-pairs showed no significant difference ($p = 0.70$). (Wang et al., 2022).

Whereas one of the studies which used a word-pair task found a significant effect of TMR when cues were presented in SO up-states (Göldi et al., 2019), the other four studies found no significant differences between the cued and uncued conditions, and as such, no significant effect of TMR (Batterink et al., 2017; Cordi et al., 2018; Henin et al., 2019; Wang et al., 2022).

Puzzle-Solving Tasks

Two of the included studies used a puzzle-solving task (Sanders & Beeman, 2021; Sanders et al., 2019), which both included four different types of puzzles; each being presented one at a time with its associated sound cue. Sanders and Beeman (2021) used a sound-puzzle memory test including two versions (with different solving difficulty) of 40 puzzles. Solved cued puzzles (M = 68.6% ±26.9%) and solved uncued puzzles (M = 70.4% ±

26.7%) showed no significant difference (p = 0.680). The results show that presentation of cues during sleep does not affect the ability to solve puzzles (Sanders & Beeman, 2021).

The pre-sleep task in Sanders et al. (2019) continued until the participants failed to solve six puzzles and the morning after they were asked to try to solve the 6 unsolved puzzles. Cued sounds from three of the six puzzles were presented to the participants during sleep. The solving of cued puzzles (M = 31.7% ± 28.3%) and uncued puzzles (M = 20.5% ± 18.9%) showed a significant difference (p = 0.002) and a significant main effect of cueing was found (p = 0.003) (Sanders et al., 2019).

When testing the effect of TMR with puzzle-solving tasks, one study (Sanders & Beeman, 2021) displayed no significant difference in solving rate between cued and uncued puzzles. Sanders et al. (2019) on the other hand, found a significant main effect of TMR and in the solving rate of cued compared to uncued puzzles.

Face-Name and Sound-Name Tasks

Two studies used name associations in their study. Whitmore et al. (2022) used 40 face-name pairs and analysed both name recall and face recognition. Whitmore et al. (2022) presented stimuli in two classes, each with a distinct sound. When seeing the face, specifically pupils, a name was played over speakers. Name recall change after sleep in the cued (M = 0.75 ± 2.03) and uncued (M = 0.21 ± 1.70) conditions showed no significant difference (p = 0.36). Face recognition change after sleep in the cued (M = 0.37 ± 0.50) and uncued (M = 0.49 ± 0.54) conditions showed no significant difference (p = 0.22) (Whitmore et al., 2022).

Witkowski et al. (2021) used 108 paintings of landscapes or skyscapes done by six different artists as stimuli. Each of the six artists in the study by Witkowski et al. (2021) had painted 18 of the included paintings and was assigned an auditory cue. In the generalization test, participants were shown new paintings and asked which of the six artists had created them. In the specificity test, the same painting slices as in the learning experience were shown together with new ones. Participants were asked to identify which of the slices had been shown before in its whole painting. The mean generalization performance in pre-sleep accuracy was 57.85% (± 2.87%) and there was no significant difference between cued and uncued accuracy (p = 0.47). Post-sleep accuracy between cued and uncued conditions showed no significant difference (p = 0.93). The mean specificity performance in pre-sleep accuracy was 60.73 % (± 2.37%). Between the cued and uncued conditions, no significant difference was found (p = 0.59). TMR effects on change in specificity accuracy between pre- and post-sleep showed a significant difference between cued and uncued conditions (p = 0.02), where accuracy after sleep was higher in the uncued condition (Witkowski et al., 2021).

No significant effect of TMR was found in either the face-name study (Whitmore et al., 2022) or the sound-name task (Witkowski et al., 2021).

Discussion

The aim of this review was to summarize studies examining TMR and auditory cues on declarative memory consolidation during SWS. A total of 18 studies were included, with the intention to answer the research question if TMR and auditory cues have a significant impact on declarative memory consolidation during SWS.

Summary of Findings

Four out of the 18 included studies found significant effects of TMR. Antony et al. (2018), Sanders et al. (2019), Van Dongen et al. (2012), and Vargas et al. (2019) all found a significant main effect of TMR during SWS when recalling or solving tasks associated with cued stimuli versus uncued stimuli. Four studies exhibited some significant results and some non-significant. Creery et al. (2015) showed a significant effect of TMR on forgetting when including the participant's level of learning before sleep. However, memory was not shown to significantly benefit from TMR when including all participants. Groch et al. (2017) found a significant effect of TMR when the task was related to prior knowledge, but not when related to non-prior knowledge. Cairney et al. (2017) found no significant effect of TMR, apart from in the forgetting of sound-speech word recall. Göldi et al. (2019) demonstrated a significant effect of TMR between the cued and uncued conditions when cues were presented to participants during SO up-states. However, no significant difference between cued and uncued stimuli was found in SO down-states. Nine studies showed no significant effect of TMR (Batterink et al., 2017; Cairney et al., 2016; Cordi et al., 2018; Henin et al., 2019; Sanders & Beeman, 2021; Schechtman et al., 2021; Wang et al., 2019, 2022; Whitmore et al., 2022). Witkowski et al. (2021) showed no significant differences in the generalization performance. However, the specificity accuracy showed a significant difference between cued and uncued conditions. Accuracy was higher in the uncued condition, which means a significant decrease in accuracy after TMR was found (Witkowski et al., 2021).

Support of Slow-Wave Sleep and Targeted Memory Reactivation

The earlier known effect of TMR and auditory cues on declarative memory is less forgetting and better memory recall (Schouten et al., 2017). SWS is believed to be essential for the consolidation of declarative memory (Ackermann & Rasch, 2014; Batterink et al., 2017). The present systematic review does not support what prior research have stated. One reason for why the present review failed to find evidence in support of the role of SWS in TMR may be the task used to measure TMR. Specifically, three of the studies that found a significant effect of SWS on TMR used an object-location task (Antony et al., 2018; Van Dongen et al., 2012; Vargas et al., 2019). It may be easier for subjects to learn object and location associations compared to other used tasks. A strength in research using object-location tasks is that humans associate objects and locations daily, which can lead to a better ability to associate these in research. On the other hand, a weakness when using other tasks may be that the task is not used daily and therefore harder for subjects to learn.

To further conclude if different tasks used to measure TMR yield differently results, more research on different tasks are needed. To compare results from different tasks may also be beneficial.

In the introduction another type of cue is mentioned, olfactory cues. According to Bar et al. (2020) auditory cues, which are tested in the included studies, can wake participants up during the cue presentation. Earlier knowledge is not specific in which cue leads to a significant effect on declarative memory consolidation. Because of this, a comparison between olfactory and auditory cues may lead to more knowledge.

Another reason for why the present review did not find support for TMR in SWS could be the participant's age. The age of the participants in these three studies also ranged from 18-33, which might have affected the results (Antony et al., 2018; Van Dongen et al., 2012; Vargas et al., 2019).

Factors such as prior knowledge and pre-sleep learning may influence the results. As shown in two studies (Creery et al., 2015; Groch et al., 2017), prior knowledge and pre-sleep learning level have been found to be correlated with the effect of TMR. Groch et al. (2017) explain that the consolidation is speeded up when prior knowledge exists because the new memory can be incorporated with the already existing memory, thus explaining why subjects with prior knowledge showed better memory recall. On the contrary, Witkowski et al. (2021) shows a decrease in learning when TMR is applied.

Limitations

One limitation of this review is that the set size (number of objects included in the study) was not included in the analysed effect of TMR. Set size influences cueing, where smaller set sizes correlated with higher cueing effects, and should therefore be included in analyses in future research (Schechtman et al., 2021). The effect of the duration of SWS was not analysed. The study by Whitmore et al. (2022) showed a significant cueing effect associated with the duration of N3. The effect of TMR can be impacted by the duration of SWS, subjects who have a longer duration of SWS might have a superior memory consolidation. Memory consolidation during SWS may have a higher quality a period into SWS, which then leads to an association between SWS duration and the subject's performance level. Furthermore, more exact results may be found when including the duration of SWS.

All subjects were analysed together in this review, which may have led to non-accurate results. The mean age of subjects (19.87-71.00) and low to high subject performance were not considered when analysing the results. Older subjects were shown to remember fewer words than younger subjects (Cordi et al., 2018), which could have been included in the analysis. As subjects get older, their brain´s ability to consolidate memories may decline, and therefore have an impact of their results. Another study, Cairney et al. (2016), demonstrated that low and high subject performance may have different effects from TMR, which was also not included in the analysis of the task results.

Societal and Ethical Aspects

Informed consent was obtained from all participants, although in Batterink et al. (2017) and Vargas et al. (2019) it is not mentioned. Eight studies informed about compensating participants for taking part in the study. The participants in Wang et al. (2019) were compensated a small amount of money if they had performed good, which can impact the truthfulness of participants' results because they may want more money. As presented in the introduction, research on TMR can help inform about the mechanisms underlying memory consolidation and might lead to improvements to future learning processes (Hu et al., 2020; Witkowski et al., 2020).

Conclusions

Fourteen out of 18 studies did not find a significant effect of TMR on declarative memory consolidation during SWS when comparing recall and forgetting of cued versus uncued stimulus. Three out of four studies which displayed a significant main effect of cueing and TMR used an object-location task, which indicates that the effect may be specific to the task used. Further research is needed to test the impact of different tasks on the effect of TMR as well as set size, age of subjects, duration of SWS, pre-sleep knowledge and performance level of subjects.

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