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Promoting Memory Consolidation During Sleep: A Meta-Analysis of Targeted Memory Reactivation

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Targeted memory reactivation (TMR) is a methodology employed to manipulate memory processing during sleep. TMR studies have great potential to advance understanding of sleep-based memory consolidation and corresponding neural mechanisms. Research making use of TMR has developed rapidly, with over 70 articles published in the last decade, yet no quantitative analysis exists to evaluate the overall effects. Here we present the first meta-analysis of sleep TMR, compiled from 91 experiments with 212 effect sizes (N = 2,004). Based on multilevel modeling, overall sleep TMR was highly effective (Hedges' g = 0.29, 95% CI [0.21, 0.38]), with a significant effect for two stages of non-rapid-eye-movement (NREM) sleep (Stage NREM 2: Hedges' g = 0.32, 95% CI [0.04, 0.60]; and slow-wave sleep: Hedges' g = 0.27, 95% CI [0.20, 0.35]). In contrast, TMR was not effective during REM sleep nor during wakefulness in the present analyses. Several analysis strategies were used to address the potential relevance of publication bias. Additional analyses showed that TMR improved memory across multiple domains, including declarative memory and skill acquisition. Given that TMR can reinforce many types of memory, it could be useful for various educational and clinical applications. Overall, the present meta-analysis provides substantial support for the notion that TMR can influence memory storage during NREM sleep, and that this method can be useful for understanding neurocognitive mechanisms of memory consolidation.

Public Significance Statement
Sensory cues can be used to reactivate associated memories during sleep and thus promote memory consolidation. This meta-analysis shows that targeted memory reactivation during sleep can improve memory performance with a small to moderate effect, and that this effect is most clearly evident when memories are reactivated during Stages 2 and 3 of non-rapid-eye-movement (NREM) sleep.

Keywords: sleep, targeted memory reactivation, memory consolidation, meta-analysis

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The idea of manipulating memories and thoughts during sleep is fascinating for neuroscientists, psychologists, and the general public. Although the idea may sound like science fiction, the past decade has witnessed an increasing number of studies wherein memory processing is directly manipulated during sleep. By covertly administering sensory cues while participants are asleep, associated memories from recent learning can be reactivated and modified. This procedure, known as targeted

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memory reactivation (TMR), gives researchers the ability to noninvasively reactivate specific memories during sleep. More generally, memory reactivation is thought to be a natural feature of sleep that underlies sleep-dependent memory consolidation and the effective preservation of memories (Paller, Mayes, Antony, & Norman, 2020).

The use of TMR in various experimental contexts has greatly advanced our understanding of causal relationships between sleep physiology and memory consolidation. TMR research is also attractive because its usefulness could extend beyond the laboratory, with high potential value for enhancing learning via offline memory processing. For example, benefits may be realized for boosting skill and language acquisition, and even enhancing psychotherapeutic effectiveness (for related discussions, see Diekelmann, 2014; Paller, 2017). Despite the influx of publications dedicated to this line of research, two imperative questions remain unanswered: What is the overall effect size aggregating across TMR studies and what are the variables that modulate the effectiveness of TMR? This meta-analysis aims to address these questions, providing quantitative estimates of the overall TMR effect as well as effects under various experimental conditions.

Spontaneous and TMR During Sleep

Memories continue to change, even after initial encoding and between episodes of deliberate rehearsal. Jenkins and Dallenbach (1924) provided initial evidence that offline sleep influenced memory processing: participants showed superior memory retention following sleep versus following an equal period of wakefulness. More recently it has become widely accepted that sleep plays an important role in consolidating and transforming memories (Diekelmann & Born, 2010; Inostroza & Born, 2013; Rasch & Born, 2013; Stickgold & Walker, 2013). For example, it has been reported that sleep can stabilize memories and render them more resistant to retroactive interference (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006), and that sleep can promote integration of newly learnt information into existing memory schema (Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010). Moreover, motivation also shapes sleep-based memory consolidation, given the demonstrated influence of emotion, reward, and future relevance on retention (Fischer & Born, 2009; Payne et al., 2015; Wilhelm et al., 2011).

One plausible mechanism supporting sleep-based memory consolidation is that prior learning experiences are spontaneously reactivated during sleep. Techniques such as single-unit recording, scalp electroencephalography (EEG), positron emission tomography (PET), and functional MRI (fMRI) allow researchers to observe brain activity during postlearning sleep. Specifically, brain activity related to wakeful encoding can spontaneously reemerge during subsequent sleep, possibly indexing memory reactivation given that the magnitude of such responses can predict postsleep memory performance (Deuker et al., 2013; Peigneux et al., 2004). These studies relied on spontaneous memory reactivation and did not directly manipulate memory reactivation during sleep. Compelling evidence for causal relationships between sleep-based memory reactivation and improved memory performance could be attained using methods to allow memory reactivation to be externally initiated and guided.

As shown in Figure 1a, TMR paradigms are characterized by three core components: First, specific learning episodes are designed so that strong associations are formed between certain sensory stimuli and learned information. In some cases, the stimuli are the main focus of learning. Second, previously learned sensory cues are presented to participants during sleep, usually during specific sleep stages identified by standard polysomnographic methods. Steps are taken to avoid arousal from sleep (e.g., sounds delivered at a low intensity over a white-noise background). Critically, reexposure to sensory cues is intended to reactivate previously learned information. The last component consists of a postsleep test upon waking. By comparing performance change scores between reactivated and nonreactivated memories, researchers can isolate the TMR effects due to the reactivation manipulation.

Although the term TMR was coined only recently (Oudiette & Paller, 2013), research using memory reminders during sleep was evident since at least the 1950s and has been periodically documented since (e.g., Aarons, 1976; Dillon & Bowles, 1976; Fox & Robbin, 1952; Guerrien, Dujardin, Mandai, Sockeel, & Leconte, 1989; Hars, Hennevin, & Pasques, 1985; Hars & Hennevin, 1987; Oswald, Taylor, & Treisman, 1960; Smith & Weeden, 1990; Tilley, 1979; Wood, Bootzin, Kihlstrom, & Schacter, 1992; for a review and discussions of these early studies, see Oudiette & Paller, 2013). These earlier studies not only aimed to reactivate prior learning established during wakefulness, but in some cases also tried to produce novel learning using sensory cues during sleep. Many of these studies were controversial and regularly dismissed on methodological grounds (e.g., Bruce, Evans, Fenwick, & Spencer, 1970). However, after Rasch, Büchel, Gais, and Born (2007) and Rudoy, Voss, Westerberg, and Paller (2009) published their seminal experiments, this line of research has grown considerably; Figure 1b documents this growth in publications on TMR.

An Overview of TMR Research

In Rasch et al. (2007), the researchers paired an olfactory cue with two learning tasks: a declarative, spatial location task and a procedural, finger-tapping task. Compared with various control conditions, reexposure of the same olfactory cue during subsequent slow-wave sleep (SWS) improved spatial recall, but not finger-tapping performance. Improvement of spatial recall was limited to cueing during SWS, in that cueing during rapid-eye-movement (REM) sleep or wakefulness did not produce noticeable change. Odor-induced memory reactivation during SWS was additionally supported by fMRI findings showing that exposure to task-relevant odors during SWS elicited hippocampal activity.

Rudoy et al. (2009) similarly reactivated spatial memories during SWS but with a set of low-intensity sounds instead of a single odor. These sounds had been presented during learning, each with an image of a semantically related object. Postsleep results showed that TMR altered memories during SWS, as locations of cued objects were recalled more accurately than were locations of uncued objects. This experiment thus made two unique contributions. First, it demonstrated that reactivation during SWS can be provoked through the auditory modality. Prior thinking was that such auditory input would largely be prevented from reaching the cortex due to gating at the thalamus, whereas olfactory processing does not pass through the thalamus (Zelano & Sobel, 2005).

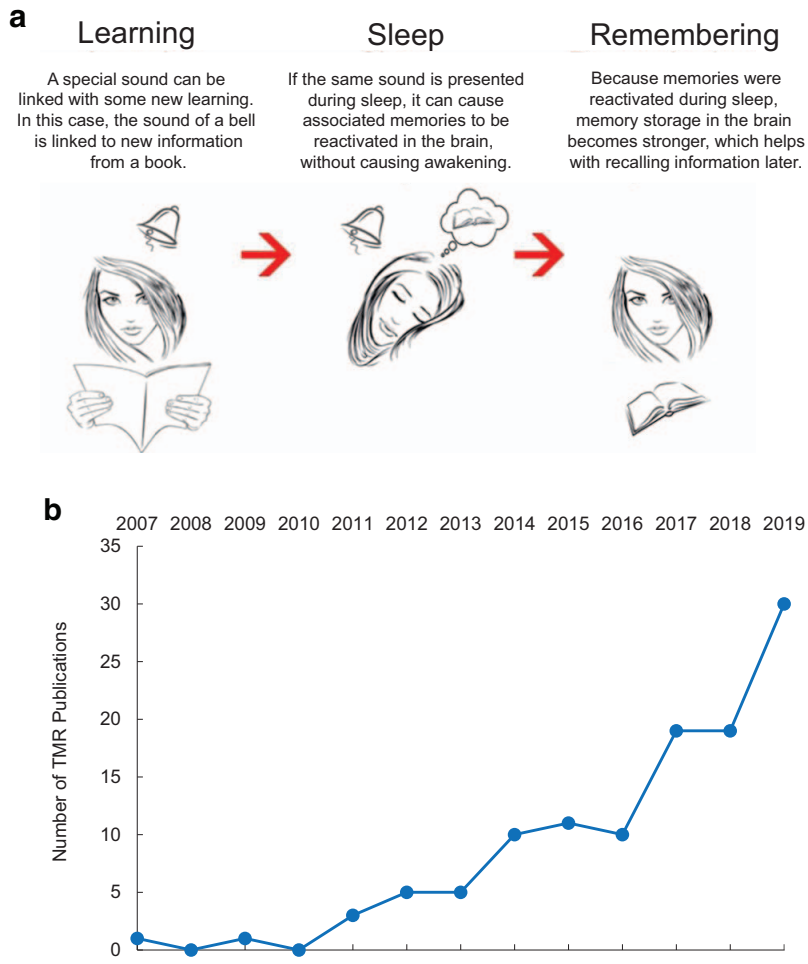

Figure 1. (a) Schematic of the typical procedure in a TMR experiment (Figure 1a is from "Do House-Elves Clean Your Brain While You Sleep?" by K. A. Paller, 2018, *Frontiers for Young Minds, 6*, p. 23. Copyright 2018 by Paller.). (b) Number of TMR articles (including both human/non-human empirical studies and review articles) published by year since Rasch et al. (2007). The last data point represents the annualized number based on number of articles published from January to June 2019. See the online article for the color version of this figure.

Second, it showed that reactivation with TMR can influence a select subset of specific memories formed during a learning episode.

These and other TMR studies enabled researchers to make strong causal inferences linking offline, sleep-based reactivation to subsequent memory performance. Furthermore, additional insights were provided about the roles of distinct sleep stages and sleep-physiology signals in relation to memory consolidation. Investigating cue-elicited brain activity during sleep can enable researchers to pinpoint neural mechanisms contributing to memory change (Ai et al., 2018; Antony, Piloto, et al., 2018; Belal et al., 2018; Cairney, Guttesen, El Marj, & Staresina, 2018; Farthouat, Gilson, & Peigneux, 2017; Schreiner, Doeller, Jensen, Rasch, & Staudigl, 2018; Schreiner, Lehmann, & Rasch, 2015; Shanahan, Gjorgieva, Paller, Kahnt, & Gottfried, 2018). Identifying relevant neural signals (e.g., slow oscillations, spindles, other brain rhythms, and fMRI activations) has now become the target of many creative experimental manipulations. Moreover, oscillatory stimulation can also be used to entrain brain rhythms to shed further light on their roles in memory (e.g., Antony & Paller, 2017; Ngo, Martinetz, Born, & Mölle, 2013; for a recent review on different stimulation methods, see Cellini & Mednick, 2019).

Given that translating basic science research to applications outside the lab setting can be advantageous, TMR provides new opportunities to boost learning beyond ordinary sleep (Diekelmann, 2014; Paller, 2017). For example, Diekelmann, Biggel, Rasch, and Born (2012) reported that a 40-min sleep with TMR enhanced memory when compared with the same length of sleep without TMR (see also Schönauer, Geisler, & Gais, 2014). Another intriguing possibility is that the benefits of TMR are cumulative and, when applied over longer periods of time, could help those who suffer from more severe memory difficulties such as neurodegenerative diseases (e.g., Westerberg et al., 2012). TMR might also aid approaches in clinical psychotherapy (Oudiette, Antony, & Paller, 2014), as using TMR during sleep could reactivate skills from a prior therapy session, helping those who suffer

from posttraumatic stress disorder, anxiety, depression, among other disorders (Paller, 2017).

To date, TMR research has been studied with many different sorts of learning. As shown in Table 1, this list includes learning paradigms such as word associative learning, visual-spatial memory, emotional memory, skill learning, vocabulary learning, grammar learning, fear conditioning/extinction, and so on. Notably, TMR has also been combined with innovative learning tasks that are not typically studied in memory research, such as phobia-exposure therapy, counterstereotype learning, multisensory integration, value-based decision making, and so on (e.g., Ai et al., 2018; Honma et al., 2016; Hu et al., 2015; Rihm, Sollberger, Soravia, & Rasch, 2016). Outside of human evidence, TMR has also been conducted with nonhuman animals including rats, mice, and even with invertebrates such as honeybees (Bendor & Wilson, 2012; Purple, Sakurai, & Sakaguchi, 2017; Rolls et al., 2013; Rothschild, Eban, & Frank, 2017; Zwaka et al., 2015). These cross-species studies provide converging evidence that memory processing can be manipulated during sleep.

A Quantitative Assessment of TMR

To date, over 90 TMR experiments have been performed on humans. These studies can inform our current understanding of what domains of learning are especially amenable to benefit from sleep reactivation. In addition, certain experimental factors may influence the effectiveness of TMR, including sleep stage when sensory cues are presented (SWS vs. REM, Lehmann, Schreiner, Seifritz, & Rasch, 2016; Rasch, Büchel, Gais, & Born, 2007; Stage NREM 2 sleep, N2 vs. REM, Laventure et al., 2016; Sterpenich et al., 2014; N2 vs. SWS, Belal et al., 2018), memory strength prior to sleep (Cairney, Lindsay, Sobczak, Paller, & Gaskell, 2016; Creery, Oudiette, Antony, & Paller, 2015), amount of prior knowledge (Groch, Schreiner, Rasch, Huber, & Wilhelm, 2017), and degree of competition between memories (Antony, Cheng, Brooks, Paller, & Norman, 2018; Oyarzún, Morís, Luque, de Diego-Balaguer, & Fuentemilla, 2017). Review articles by Oudiette and Paller (2013), Schouten, Pereira, Tops, and Louzada (2017); Cellini and Capuozzo (2018), and Paller et al. (2020) have aptly summarized the breadth of topics investigated using the procedure, yet no quantitative summary of experimental effects exists. Narrative reviews typically adopt a vote-counting approach in summarizing existing evidence, taking TMR results as either significant or not (e.g., Table 1 from Cellini & Capuozzo, 2018; Tables 2–4 from Schouten et al., 2017). Despite its appealing simplicity, this vote-counting approach can be misleading because null results and inconsistent findings are attributed to sampling errors or procedural variations in a descriptive rather than in a quantitative manner (Siddaway, Wood, & Hedges, 2019). In contrast, meta-analytic approaches synthesize all available effect sizes, while taking statistical power and precision of estimates into consideration to quantitatively estimate the effectiveness of specific procedures. Moreover, by partitioning effect sizes into different categories, moderator analyses in a meta-analysis can advance theoretical understanding of how experimental factors may influence memory consolidation, such as sleep stages (NREM vs. REM), learning types (declarative vs. skill learning), and how learning outcomes are measured (recall vs. recognition etc.).

Here, we aggregated all available data sets to provide evidence relevant for assessing the effect size of memory benefits produced by TMR. First, we aimed to provide an overall estimate of the TMR effect. We then planned a series of moderator analyses to address the aforementioned questions. Our foremost research question concerns whether TMR is specific to certain *cueing stages,* such as N2, SWS, REM, and wakeful states. Another potentially important question never directly examined in any single study is whether TMR effectiveness varies as a function of sleep duration (ranging from 0.67 hr to 8 hr). This variable can be examined in a meta-analysis because it aggregates studies with different sleep durations.

We compared effects on *different types of learning*, based on current theorizing in memory research. Learning tasks were categorized into either declarative memory, skill acquisition, conditioning, or other types of learning. The last category includes studies that cannot easily be grouped into conventional categories, such as phobia-exposure therapy, social learning, multisensory integration, value-based decision making, and so forth In addition to learning tasks, we coded how TMR may differentially influence various *outcome measurements* such as (a) recall that relies on cued or free recall testing; (b) recognition in discriminating old and new items; (c) behavioral performance when memory is not explicitly probed, such as speed and accuracy during reaction time (RT)-based tasks, or problem solving; (d) subjective ratings when participants are asked to self-report how they feel and think regarding mnemonic materials; and (e) skin conductance response (SCR).

In another analysis, we investigated whether TMR effects varied as a function of *within-versus between-subjects* designs, and whether TMR effectiveness differed as a function of *sensory stimulation modality* (auditory_verbal, auditory_nonverbal, or olfactory cues). Our hope is that the results from these analyses will serve as a resource for future parameter selection and lessen ambiguity concerning boundary conditions of effective TMR application.

Lastly, acknowledging that learning tasks vary, we conducted *focal analyses* to examine subsets of studies with homogeneous learning tasks combined with NREM TMR. We identified the following topics: *spatial learning, associative learning, language acquisition, false memories,* and *skill learning*. We additionally investigated *cognitive bias modifications, emotional memories,* and *fearful memories,* given the potential clinical benefit of improving symptoms associated with mood- and trauma-related disorders. For example, because TMR can reactivate and bias memories regarding potential interpretation of ambiguous scenes (Groch et al., 2016, 2017), it may be useful for reducing habitual negative biases observed in depressive and anxiety disorders (Hallion & Ruscio, 2011). Compared with overall analyses that span a range of different tasks and conditions, focal analyses with relatively homogenous procedures can be advantageous because estimated effect sizes can help guide future research on similar topics.

Method

We relied on two meta-analysis handbooks, Lipsey and Wilson (2001) and Borenstein, Hedges, Higgins, and Rothstein (2011), as our primary references in each stage of implementing the meta-analysis. We also followed the Preferred Reporting Items for

Table 1
Sample, Experimental Characteristics, and Effect Sizes Information of TMR Experiments/Tasks Included in the Meta-Analysis

	Sample characteristics				TMR experimental characteristics							Effect sizes				
References	Sample size	Female ratio	Age	Country	Cueing stages	Sleep length	Memory task	Learning type	Focal analyses	Design	Cueing modality	Hedges' *g*	95% CI LL	95% CI UL	*Z*	*p*
Dillon & Babor, 1970	12	.00	20.5	U.S.	Unspecified	8	Word-word learning	Declarative		Within	Verbal	.40	−.17	.97	1.388	.165
Tilley, 1979 N2	8	NA	NA	U.S.	N2	8	Word-picture learning	Declarative	Associative	Within	Verbal	1.12	.29	1.95	2.658	.008
Tilley, 1979 REM	8	NA	NA	U.S.	REM	8	Word-picture learning	Declarative		Within	Verbal	.17	−.46	.79	.525	.600
^Guerrien et al., 1989	10	.00	20.0	U.S.	REM	8	Morse code learning	Declarative		Between	Nonverbal	3.47	1.58	5.36	3.601	<.001
^Smith & Weeden, 1990	10	NA	19.4	Canada	REM	8	Wff n' Proof Logic Game	Declarative		Between	Nonverbal	3.17	1.39	4.95	3.482	<.001
Rasch et al., 2007 Exp. 1 spatial	18	.56	24.1	Germany	SWS	7.5	Spatial location	Declarative	Spatial	Within	Olfactory	.69	.19	1.18	2.717	.007
Rasch et al., 2007 Exp. 1 skill					SWS	7.5	Finger sequence tapping	Skill	Skill	Within	Olfactory	−.08	−.52	.37	−.339	.734
Rasch et al., 2007 Exp. 3 spatial	17	.53	25.0	Germany	REM	7.5	Spatial location	Declarative		Within	Olfactory	−.05	−.51	.40	−.236	.813
Rasch et al., 2007 Exp. 3 skill					REM	7.5	Finger sequence tapping	Skill		Within	Olfactory	−.21	−.67	.25	−.905	.366
[1]Rasch et al., 2007 Exp. 5	12	.50	25.4	Germany	SWS	1.5	Spatial location	Declarative	Spatial	Within	Olfactory	.64	.05	1.22	2.136	.033
Rudoy et al., 2009	12	.83	21.5	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.48	−.08	1.04	1.671	.095
Diekelmann, Büchel, Born, & Rasch, 2011	12	.17	22.3	Germany	SWS	.67	Spatial location	Declarative	Spatial	Within	Olfactory	.74	.08	1.40	2.207	.027
Donohue & Spencer, 2011	32	.63	20.8	U.S.	Unspecified	8	Word-word learning	Declarative		Between	Nonverbal	.00	−.68	.68	.000	1.000
Antony, Gobel, O'Hare, Reber, & Paller, 2012	16	.38	21.0	U.S.	SWS	1.5	Finger sequence tapping	Skill	Skill	Within	Nonverbal	.46	−.03	.96	1.836	.066
Ritter, Strick, Bos, van Baaren, & Dijksterhuis, 2012	30	.87	21.3	Netherlands	Unspecified	8	Creative solutions	Declarative		Between	Olfactory	1.07	.31	1.82	2.780	.005
van Dongen et al., 2012	22	.73	22.5	Netherlands	SWS	2	Spatial location	Declarative	Spatial	Within	Nonverbal	−.21	−.61	.20	−.989	.323
Fuentemilla et al., 2013	9	.67	41.0	Spain	SWS	8	Sound-word learning	Declarative	Associative	Within	Nonverbal	.70	.03	1.38	2.045	.041
Hauner, Howard, Zelano, & Gottfried, 2013	15	.53	24.5	U.S.	SWS	1.5	Fear extinction	Conditioning	Fear	Within	Olfactory	.51	.00	1.03	1.968	.049
Oudiette, Antony, Creery, & Paller, 2013	15	.60	20.7	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.24	−.25	.72	.962	.336
Cairney, Durrant, Hulleman, & Lewis, 2014 neutral	15	.80	20.4	UK	SWS	1.5	Spatial location neutral picture	Declarative	Spatial	Within	Nonverbal	.08	−.40	.56	.325	.745
Cairney et al., 2014 Negative					SWS	1.5	Spatial location negative picture	Declarative	Emotion	Within	Nonverbal	.19	−.30	.67	.758	.449
Cordi, Diekelmann, Born, & Rasch, 2014	16	.63	23.9	Switzerland	REM	4	Spatial location	Declarative		Within	Olfactory	.08	−.38	.55	.346	.729
Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2014	16	.50	24.8	UK	SWS	8	SRTT	Skill	Skill	Within	Nonverbal	.87	.31	1.43	3.064	.002
Cox, Hofman, de Boer, & Talamini, 2014	28	.89	20.1	Netherlands	SWS	2	Spatial location	Declarative	Spatial	Within	Olfactory	.03	−.33	.39	.137	.891
Rihm, Diekelmann, Born, & Rasch, 2014 spatial	21	.71	23.4	Switzerland	SWS	7.5	Spatial location	Declarative	Spatial	Between	Olfactory	.95	.08	1.82	2.134	.033

Table 1 (*continued*)

References	Sample characteristics				TMR experimental characteristics							Effect sizes				
	Sample size	Female ratio	Age	Country	Cueing stages	Sleep length	Memory task	Learning type	Focal analyses	Design	Cueing modality	Hedges' *g*	95% CI LL	95% CI UL	*Z*	*p*
Rihm et al., 2014 unpublished false memories					SWS	7.5	DRM	Declarative	False memories	Between	Olfactory	.10	−.72	.93	.245	.807
Schönauer et al., 2014	28	NA	22.3	Germany	SWS	3	Finger sequence tapping	Skill	Skill	Within	Nonverbal	.47	.09	.85	2.432	.015
Sterpenich et al., 2014 N2	28	.50	21.6	Belgium	N2	8	Sound-negative/neutral picture learning	Declarative	Emotion	Between	Nonverbal	.26	−.46	.98	.703	.482
Sterpenich et al., 2014 REM	28	.50	21.6	Belgium	REM	8	Sound-negative/neutral picture learning	Declarative		Between	Nonverbal	−1.01	−1.78	−.24	−2.586	.010
Ai et al., 2015	46	.59	22.0	China	SWS	1.5	Fear extinction	Conditioning	Fear	Between	Nonverbal	−.71	−1.30	−.12	−2.370	.018
Creery, Oudiette, Antony, & Paller, 2015	20	.60	21.0	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.25	−.18	.68	1.157	.247
^He et al., 2015 3 min	35	.49	23.8	China	SWS	4	Fear extinction	Conditioning	Fear	Between	Nonverbal	1.94	1.15	2.73	4.805	<.001
^He et al., 2015 10 min	31	.55	23.6	China	SWS	4	Fear extinction	Conditioning	Fear	Between	Nonverbal	4.83	3.44	6.21	6.838	<.001
Hu et al., 2015	38	.50	21.8	U.S.	SWS	1.5	Counter-bias learning	Others		Within	Nonverbal	.51	.18	.84	3.011	.003
Rihm & Rasch, 2015 N2	14	1.00	23.3	Switzerland	N2	4	Evaluative conditioning	Conditioning	Emotion	Within	Nonverbal	−.11	−.61	.39	−.445	.656
Rihm & Rasch, 2015 REM	16	1.00	23.3	Switzerland	REM	4.5	Evaluative conditioning	Conditioning		Within	Nonverbal	.07	−.41	.55	.287	.774
Schreiner & Rasch, 2015a	15	.53	25.1	Switzerland	SWS	3	Word-word learning (foreign)	Declarative	Language	Within	Verbal	.50	−.04	1.05	1.821	.069
Schreiner, Lehmann, et al., 2015 control	16	.63	23.3	Switzerland	SWS	3	Word-word learning (foreign)	Declarative	Language	Within	Verbal	.82	.28	1.37	2.962	.003
Schreiner, Lehmann, et al., 2015 correct	14	.71	22.7	Switzerland	SWS	3	Word-word learning (foreign)	Declarative	Language	Within	Verbal	.77	.20	1.34	2.659	.008
Schreiner, Lehmann, et al., 2015 false	13	.69	21.2	Switzerland	SWS	3	Word-word learning (foreign)	Declarative	Language	Within	Verbal	.95	.32	1.57	2.964	.003
Cairney, Lindsay, Sobczak, Paller, & Gaskell, 2016 direct	30	.53	19.9	UK	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.42	.05	.78	2.247	.025
Cairney et al., 2016 indirect					SWS	1.5	Picture-word learning	Declarative	Associative	Within	Nonverbal	−.03	−.38	.32	−.167	.867
Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2016	22	.36	23.5	UK	SWS	8	SRTT	Skill	Skill	Within	Nonverbal	.40	−.03	.83	1.837	.066
Diekelmann, Born, & Rasch, 2016	36	.53	21.9	Germany	SWS	8	SRTT	Skill	Skill	Between	Olfactory	.35	−.31	1.00	1.044	.297
Groch et al., 2016 adolescent	21	.29	12.3	Switzerland	SWS	8	CBM	Declarative	CBM	Within	Verbal	.31	−.11	.74	1.440	.150
Groch et al., 2016 adult	19	.74	22.2	Switzerland	SWS	8	CBM	Declarative	CBM	Within	Verbal	.30	−.15	.75	1.300	.193
Honma et al., 2016	16	.75	20.1	U.S.	SWS	8	Rubber hand illusion	Others		Within	Nonverbal	.98	.38	1.58	3.209	.001
Laventure et al., 2016 N2	39	.41	25.1	Canada	N2	8	Finger sequence tapping	Skill	Skill	Between	Olfactory	.94	.27	1.61	2.734	.006
Laventure et al., 2016 REM	37	.41	24.7	Canada	REM	8	Finger sequence tapping	Skill		Between	Olfactory	.27	−.38	.93	.825	.409
Lehmann, Schreiner, Seifritz, & Rasch, 2016 SWS emotion	21	.76	22.1	Switzerland	SWS	3	Word-emotional picture learning	Declarative	Emotion	Within	Verbal	.54	.10	.98	2.394	.017
Lehmann et al., 2016 SWS neutral					SWS	3	Word-neutral picture learning	Declarative	Associative	Within	Verbal	.16	−.25	.57	.756	.450
Lehmann et al., 2016 REM emotion	20	.80	22.3	Switzerland	REM	6	Word-emotional picture learning	Declarative		Within	Verbal	.21	−.22	.63	.944	.345
Lehmann et al., 2016 REM neutral					REM	6	Word-neutral picture learning	Declarative		Within	Verbal	−.25	−.68	.18	−1.150	.250

(*table continues*)

Table 1 (*continued*)

	Sample characteristics				TMR experimental characteristics							Effect sizes				
References	Sample size	Female ratio	Age	Country	Cueing stages	Sleep length	Memory task	Learning type	Focal analyses	Design	Cueing modality	Hedges' *g*	95% CI LL	95% CI UL	*Z*	*p*
Rihm, Sollberger, Soravia, & Rasch, 2016	36	.89	25.7	Switzerland	SWS	1.5	Phobia exposure therapy	Others	Fear	Between	Olfactory	.21	−.43	.85	.650	.516
Batterink & Paller, 2017	35	.66	22.4	U.S.	SWS	1.5	Artificial language learning	Declarative	Language	Between	Verbal	.76	.09	1.44	2.231	.026
Batterink et al., 2017 nonverbal	16	.54	20.7	U.S.	SWS	1.5	Sound-word learning (foreign)	Declarative	Language	Within	Nonverbal	−.07	−.54	.39	−.307	.759
Batterink et al., 2017 verbal	10	.54	20.7	U.S.	SWS	1.5	Word-word learning (foreign)	Declarative	Language	Within	Verbal	−.03	−.60	.53	−.118	.906
Cairney, Sobczak, Lindsay, & Gaskell, 2017 Exp. 1 nonverbal	28	.00	20.3	UK	SWS	8	Sound-word learning	Declarative	Associative	Within	Nonverbal	.47	.09	.85	2.428	.015
Cairney et al., 2017 Exp. 1 verbal					SWS	8	Speech-word learning	Declarative	Associative	Within	Verbal	.55	.17	.94	2.798	.005
Cairney et al., 2017 Exp. 2 nonverbal	23	.00	21.0	UK	SWS	8	Sound-word learning	Declarative	Associative	Within	Nonverbal	.54	.11	.96	2.479	.013
Cairney et al., 2017 Exp. 2 verbal					SWS	8	Speech-word learning	Declarative	Associative	Within	Verbal	−.18	−.58	.21	−.905	.365
Farthouat, Gilson, & Peigneux, 2017	14	.64	22.4	Belgium	SWS	1.5	Word-word learning	Declarative	Associative	Within	Verbal	.26	−.26	.77	.980	.327
Groch, Preiss et al., 2017 control	13	.31	13.2	Switzerland	SWS	8	CBM	Declarative	CBM	Within	Verbal	.03	−.49	.56	.120	.904
Groch, Preiss et al., 2017 social anxiety	13	.62	13.4	Switzerland	SWS	8	CBM	Declarative	CBM	Within	Verbal	.16	−.36	.68	.604	.546
Groch, Schreiner, Rasch, Huber, & Wilhelm, 2017	16	.69	20.3	Switzerland	SWS	8	Picture-word learning	Declarative	Associative	Within	Verbal	.14	−.36	.63	.534	.594
Hennies, Lambon Ralph, Durrant, Cousins, & Lewis, 2017	28	.39	22.7	UK	SWS	8	Memory abstraction	Declarative		Between	Nonverbal	−1.00	−1.77	−.24	−2.570	.010
Oyarzún, Morís, Luque, de Diego-Balaguer, & Fuentemilla, 2017 contiguous	22	.73	23.2	Spain	SWS	1	Spatial location	Declarative	Spatial	Within	Nonverbal	.24	−.16	.65	1.171	.242
Oyarzún et al., 2017 delayed	28	.71	23.2	Spain	SWS	1	Spatial location	Declarative	Spatial	Within	Nonverbal	−.44	−.82	−.06	−2.285	.022
Pereira et al., 2017	29	.62	24.2	Brazil	N2	1.5	Finger sequence tapping	Skill	Skill	Between	Tactile	−.57	−1.30	.16	−1.541	.123
Tamminen, Lambon Ralph, & Lewis, 2017	20	.80	19.3	UK	SWS	1.5	Word-word learning	Declarative	Associative	Within	Verbal	−.13	−.56	.29	−.622	.534
Ai et al., 2018	47	.85	23.4	China	N2	1.5	Auction decision making	Others		Within	Verbal	.66	.35	.97	4.124	<.001
Antony, Cheng et al., 2018 separate spatial	30	.73	26.5	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.37	.01	.73	2.007	.045
Antony, Cheng et al., 2018 separate associative					SWS	1.5	Sound-picture learning	Declarative	Associative	Within	Nonverbal	−.04	−.38	.31	−.200	.842
Antony, Cheng et al., 2018 competitive spatial	30	.70	26.5	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	−.17	−.52	.18	−.949	.343

Table 1 (*continued*)

References	Sample characteristics				TMR experimental characteristics							Effect sizes				
	Sample size	Female ratio	Age	Country	Cueing stages	Sleep length	Memory task	Learning type	Focal analyses	Design	Cueing modality	Hedges' *g*	95% CI LL	95% CI UL	*Z*	*p*
Antony, Cheng et al., 2018 competitive associative					SWS	1.5	Sound-picture learning	Declarative	Associative	Within	Nonverbal	−.09	−.44	.26	−.493	.622
Antony, Piloto et al., 2018 spatial	18	.50	21.8	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.54	.06	1.01	2.223	.026
Antony, Piloto et al., 2018 associative					SWS	1.5	Sound-picture learning	Declarative	Associative	Within	Nonverbal	.10	−.34	.54	.443	.658
Ashton, Cairney, & Gaskell, 2018 negative associative	19	.68	22.0	UK	SWS	1.5	Sound-negative picture learning	Declarative	Emotion	Within	Nonverbal	.03	−.40	.46	.150	.881
Ashton et al., 2018 neutral associative					SWS	1.5	Sound-neutral picture learning	Declarative	Associative	Within	Nonverbal	.10	−.33	.53	.447	.655
Ashton et al., 2018 negative spatial					SWS	1.5	Spatial location_ negative picture	Declarative	Emotion	Within	Nonverbal	−.33	−.77	.11	−1.457	.145
Ashton et al., 2018 neutral spatial					SWS	1.5	Spatial location_ neutral picture	Declarative	Spatial	Within	Nonverbal	−.22	−.66	.22	−.987	.324
Cairney, Guttesen, El Marj, & Staresina, 2018	27	.70	19.7	UK	SWS	1.5	Word-picture learning	Declarative	Associative	Within	Verbal	.50	.09	.90	2.420	.016
Cordi, Schreiner, & Rasch, 2018	23	.65	71.0	Switzerland	SWS	3	Word-word learning (foreign)	Declarative	Language	Within	Verbal	.06	−.33	.46	.309	.758
Johnson, Scharf, & Westlake, 2018	9	.56	27.9	U.S.	SWS	8	Target throwing	Skill	Skill	Between	Nonverbal	1.85	.36	3.34	2.441	.015
Klinzing et al., 2018 acetycholine	15	.00	23.9	Germany	SWS	.67	Spatial location	Declarative	Spatial	Within	Olfactory	.42	−.08	.92	1.628	.103
Klinzing et al., 2018 control	14	.00	23.9	Germany	SWS	.67	Spatial location	Declarative	Spatial	Within	Olfactory	.98	.36	1.59	3.128	.002
Seibold, Rasch, Born, & Diekelmann, 2018	19	.63	22.1	Germany	SWS	.67	Spatial location	Declarative	Spatial	Within	Olfactory	.22	−.22	.66	.969	.333
Shanahan, Gjorgieva, Paller, Kahnt, & Gottfried, 2018	18	.61	25.1	U.S.	SWS	1.25	Spatial location	Declarative	Spatial	Within	Olfactory	.33	−.15	.81	1.355	.175
Shimizu et al., 2018	37	.43	25.1	U.S.	SWS	1.5	Spatial navigation	Declarative	Spatial	Between	Nonverbal	1.34	.64	2.05	3.750	<.001
Simon, Gómez, & Nadel, 2018	18	.78	20.2	U.S.	SWS	8	Directed forgetting	Declarative		Within	Nonverbal	.74	.24	1.25	2.891	.004
[2]Strachan et al., 2019 preprint	23	.52	21.3	UK	SWS	1.5	Trust learning	Others		Within	Nonverbal	.12	−.28	.52	.584	.559
Göldi & Rasch, 2019	66	NA	21.9	Switzerland	Unspecified	8	Word-word learning	Declarative		Within	Verbal	−.09	−.33	.15	−.752	.452
Göldi et al., 2019	16	.81	20.9	Switzerland	SWS	3	Word-word learning (foreign)	Declarative	Language	Within	Verbal	.52	.02	1.02	2.030	.042
Humiston & Wamsley, 2019	31	.52	19.5	U.S.	SWS	1.5	Counter-bias learning	Others		Within	Nonverbal	−.06	−.41	.29	−.333	.739
Johnson et al., 2019	25	.52	26.0	U.S.	SWS	1	Target throwing	Skill	Skill	Between	Nonverbal	.82	.00	1.63	1.966	.049

(*table continues*)

Table 1 (*continued*)

	Sample characteristics				TMR experimental characteristics							Effect sizes				
References	Sample size	Female ratio	Age	Country	Cueing stages	Sleep length	Memory task	Learning type	Focal analyses	Design	Cueing modality	Hedges' *g*	95% CI LL	95% CI UL	*Z*	*p*
Vargas, Schechtman, & Paller, 2019	24	NA	21	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.24	−.17	.64	1.148	.251
Wang, Antony, et al., 2019	24	.58	22.3	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.30	−.10	.69	1.466	.143
Bar et al., 2019 preprint	19	.58	27.4	Israel	SWS	2	Spatial location	Declarative	Spatial	Within	Olfactory	.21	−.23	.64	.934	.350
Cheng et al., 2019	20	.70	20.5	U.S.	SWS	1.5	Motor learning	Skill	Skill	Within	Nonverbal	.53	.08	.99	2.280	.023
Gao et al., 2019 abstract	41	.70	21.2	U.S.	SWS	8	Lecture learning	Declarative		Between	Nonverbal	.39	−.30	1.07	1.110	.267
Schechtman et al., 2019, preprint	31	.68	20.8	U.S.	SWS	1.5	Spatial location	Declarative	Spatial	Within	Nonverbal	.53	.16	.89	2.809	.005
Cousins, 2014, Dissertation Chapter 5, Exp. 1	15	.73	20.3	UK	SWS	8	DRM	Declarative	False memories	Within	Nonverbal	.13	−.35	.61	.513	.608
Cousins, 2014, Dissertation Chapter 5, Exp. 2	16	.44	23.9	UK	SWS	8	DRM	Declarative	False memories	Within	Verbal	−.20	−.67	.27	−.831	.406
Konrad, 2014, Dissertation Exp. 3	11	.00	22.5	Germany	SWS	1	Method of Loci	Declarative	Associative	Within	Nonverbal	.10	−.44	.65	.369	.712
Vargas, 2016, Dissertation Exp. 1	14	NA	25.5	U.S.	SWS	1.5	Reality-monitoring	Declarative	False memories	Within	Nonverbal	.04	−.46	.53	.139	.889
Vargas, 2016, Dissertation Exp. 2	16	NA	22.5	U.S.	SWS	1.5	Word-picture learning	Declarative	Associative	Within	Verbal	−.03	−.50	.43	−.138	.890

Note. NA = not available; N2 = stage NREM 2 sleep; TRM = targeted memory reactivation; REM = rapid eye movement; SWS = slow-wave sleep. Sleep length is given in hours. SRTT = serial reaction time task; DRM = Deese-Roediger-McDermott false memory task; CBM = cognitive bias modification; CI = confidence interval. UL and LL refer to the upper and lower limit of the 95% confidence interval of effect sizes. When age range instead of mean age was reported, we calculated the midpoint of the age range as an estimate of the sample's mean age. ˆ Indicates statistical outliers based on studentized residuals. For details of outlier and influence case analyses, please see online supplementary material: Rasch et al. (2007) Exp. 5, the effect size was calculated based on the comparison between sleep- and wake-TMR 2, Strachan et al., 2019, preprint was coded as "unpublished" in the analyses as we finished the literature search in June, 2019. This article was subsequently published in July, 2019, and was updated in the reference list as Strachan et al. (2019).

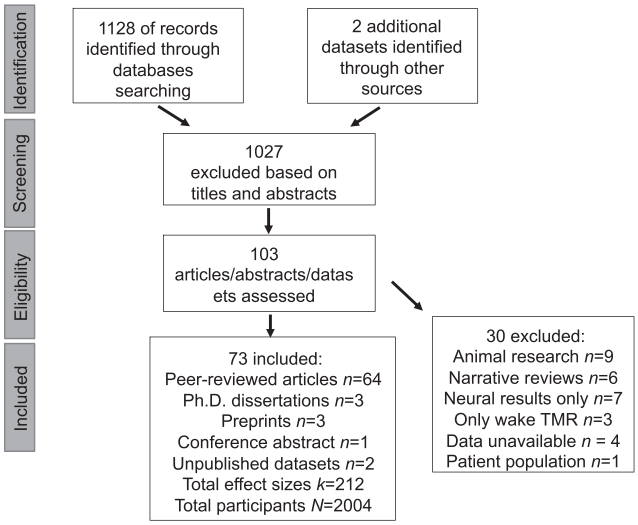

Figure 2. A PRISMA flow chart of literature search and inclusion.

Systematic Reviews and Meta-Analyses (PRISMA) statement of Moher, Liberati, Tetzlaff, and Altman (2009) and their 27-item meta-analysis checklist to guide our meta-analysis and preparation of the article (see online supplementary material for the PRISMA statement).

Literature Search

Figure 2 depicts a PRISMA flowchart of the literature search. To strive for an exhaustive list of data sets, we followed three steps. First, we conducted searches with online databases including Web of Science, PsycINFO (via ProQuest, including journals/books/dissertations/theses), PubMed, and bioRxiv/PsyArxiv through June 2019 with key words referring to *memory reactivation* and *sleep*. Exact key words using Boolean operators are (*targeted memory reactivation* OR *memory reactivation* OR *memory cueing* OR *memory replay)* AND *(sleep* OR *N2* OR *slow-wave sleep* OR *SWS* OR *NREM* OR *REM*). In this way, we collected (a) peer-reviewed published and in-press research articles, (b) unpublished dissertations/theses, and (c) preprints uploaded to repositories (i.e., bioRxiv, PsyArxiv). Unpublished dissertations and preprints were included to attempt to weigh against publication bias. In the second step, we contacted researchers who had previously published on TMR or on sleep and memory consolidation to solicit unpublished data sets and underreview articles. We included these identified unpublished data sets and articles in the meta-analysis (some of the articles were either subsequently published or overlapping with unpublished dissertations identified earlier). In Step 3, we checked the reference sections from related review articles to identify missing references (Aarons, 1976; Cellini & Capuozzo, 2018; Diekelmann & Born, 2010; Oudiette & Paller, 2013; Rasch & Born, 2013; Schouten et al., 2017; Stickgold & Walker, 2013). All authors checked and agreed on the final reference list.

Inclusion/Exclusion Criteria

We applied the following inclusion/exclusion criteria to select studies for this meta-analysis. First, sensory stimulation must have been applied to reactivate prior learning instead of inducing novel learning or EEG activity change (e.g., Antony & Paller, 2017; Arzi et al., 2012, 2014; Dillon & Bowles, 1976; Ngo et al., 2013; Züst, Ruch, Wiest, & Henke, 2019). Second, given that our primary research question concerns sleep TMR, we excluded articles that only examined wake TMR (Alm, Ngo, & Olson, 2019; Schreiner & Rasch, 2015b; Tambini, Berners-Lee, & Davachi, 2017). Third, we only included studies that used human participants, excluding the few nonhuman animal TMR studies that have been published (e.g., Barnes & Wilson, 2014; Bendor & Wilson, 2012; Purple et al., 2017; Rolls et al., 2013). Fourth, studies must have reported behavioral effects, excluding articles that only examined neural mechanisms of TMR (e.g., Batterink, Creery, & Paller, 2016). Lastly, sufficient statistical details must have been available to extract relevant effect sizes (means, *SD*, *F*, and *t*). When statistical details were not reported in the text, we either contacted corresponding authors to request relevant data or extracted needed data from published figures in the article using "metaDigitise" (Pick, Nakagawa, & Noble, 2019).

Coding of Study Characteristics

Coding was conducted by the first author and double-checked by the second author. Disagreements were resolved through discussions. Interrater reliability was calculated with Cohen's Kappa coefficient (Cohen, 1960), using "ICC" package in R. In general, raters showed high consistency, with a range of κ from 0.94 to 1.00. We coded each experiment based on three aspects: publication status, sample characteristics, and experimental design characteristics. For publication status, we coded each experiment with (a) publication year; (b) publication type (peer-reviewed journal article, dissertation, conference abstract, preprint, and unpublished dataset); and (c) publication status (journal articles coded as published, with all remaining coded as unpublished). Regarding sample characteristics, we coded each experiment with (a) sample size, (b) gender ratio, (c) mean age, and (d) country of origin.

Regarding experimental design characteristics, we first coded each experiment based on TMR cueing stages, such that whether TMR was administered during N2, SWS, REM, unspecified (i.e., when TMR was administered without EEG monitoring), or wakefulness. If cues were delivered during both N2 and SWS, the study was coded as SWS, and all N2 and SWS TMR studies were further combined as NREM. We then coded sleep duration as a continuous variable on how long participants were given to sleep, ranging from 0.67 hr to 8 hr.

Learning tasks used in each experiment were categorized as declarative memory, skill learning, conditioning, and other types of learning. We then examined each outcome measurement, and coded them into one of five categories: recall, recognition, behavioral performance, subjective ratings, and SCR.

Lastly, we coded whether TMR was administered using a between- or a within-subject design, and which sensory modality was used in TMR cueing, including auditory_nonverbal versus auditory_verbal versus olfactory cues.

Following moderator analyses, we conducted focal analyses based on tasks and experimental conditions of interest, as opposed to the all-inclusive nature of the main analyses. Specifically, we selected TMR studies focusing on spatial learning that used spatial object-location tasks and navigation tasks (e.g., Rasch et al., 2007;

Rudoy, Voss, Westerberg, & Paller, 2009; Shanahan et al., 2018; Shimizu et al., 2018). A second topic covered associative learning tasks in which participants learned stimuli pairings (e.g., spoken words/sounds to be paired with words/pictures, e.g., Cairney et al., 2018; Cairney, Sobczak, Lindsay, & Gaskell, 2017; Fuentemilla et al., 2013). A third topic included TMR studies that examined language learning, including foreign vocabulary acquisition, grammatical learning, and generalization (e.g., Batterink & Paller, 2017; Cordi, Schreiner, & Rasch, 2018; Schreiner & Rasch, 2015a, 2017). For false memories, identified tasks typically used either Deese-Roediger-McDermott procedures or reality monitoring tasks (Cousins, 2014, unpublished dissertation; Rihm, Diekelmann, Born, & Rasch, 2014, unpublished dataset; Vargas, 2016, unpublished dissertation). In addition to these analyses focused on declarative memories, we examined studies involving skill learning because of their implications in enhancing motor performance and thus motor rehabilitation. We planned to focus on performance measures of reaction speed and accuracy (e.g., Antony et al., 2012; Cousins et al., 2016; Laventure et al., 2016), as well as explicit knowledge of motor sequences in skill learning (e.g., Cousins, El-Deredy, Parkes, Hennies, & Lewis, 2014; Diekelmann, Born, & Rasch, 2016). Lastly, we synthesized effect sizes from studies with translational implications in clinical settings, namely cognitive bias modification (e.g., Groch et al., 2016; Groch et al., 2017), emotional memories (e.g., Ashton, Cairney, & Gaskell, 2018; Cairney, Durrant, Hulleman, & Lewis, 2014; Lehmann et al., 2016; Rihm & Rasch, 2015), and fearful memories (e.g., Ai et al., 2015; Hauner, Howard, Zelano, & Gottfried, 2013; He et al., 2015). Coding of study characteristics and categorization of focal analyses can be found in Table 1 and in online supplementary material.

Effect Size Calculation

To calculate effect sizes, we used equations recommended in Dunlap, Cortina, Vaslow, and Burke (1996), Lakens (2013, with spreadsheet available at https://osf.io/vbdah/), and Morris and DeShon (2002). In TMR research, effect sizes are best captured by comparing post- minus presleep performance changes between cued versus uncued conditions in terms of standardized mean differences (i.e., the Cohen's *d* family). For both within- and between-subjects designs, we calculated effect sizes based on mean and *SD*s as a common metric to (a) allow direct comparisons and moderator analyses across within- and between-subjects designs; and (b) avoid the risk of inflated effect sizes and false-positive rates (Dunlap et al., 1996; Lakens, 2013, Table 1; Morris & DeShon, 2002). Across the whole sleep TMR dataset, 96.7% (205 out of 212) of effect sizes were calculated based on means and *SD*s.

In a within-subject TMR study, participants receive both cued and uncued treatments within a single sleep session (e.g., Rudoy et al., 2009), or in two sleep sessions if the design calls for counterbalanced sleep manipulations (Rasch et al., 2007). For within-subject designs, we searched for post- minus presleep memory change scores for cued and uncued conditions and their associated *SD*s, respectively. Means and associated *SD*s for cued and uncued conditions' change scores were used to calculate the TMR cueing effect in terms of Cohen's *d*av, as recommended for meta-analyses (Lakens, 2013, Formula 10 and Table 1). If means and *SD*s (or *SE*s) were not reported nor available, then we searched for statistical tests that examined the effects. Such statistical tests can be reported in one of the three following forms: (a) a within-subject *ANOVA* that reported a 2 (pre- vs. postsleep) × 2 (cued vs. uncued) interaction; (b) a paired-sample *t* test that compared changes in memory scores (over sleep) for cued and uncued items; or (c) a paired-sample *t* test that compared cued versus uncued postsleep memory scores (in these cases, the postsleep memory performance was scaled to the corresponding presleep memory performance, see Rasch et al., 2007). Based on these statistics, we transformed the reported *F* values from the two-way interaction (with one degree of freedom tests), or the *t*-values from the paired-sample *t* tests to Cohen's *dz* (see Lakens, 2013, Formula 7; Morris & DeShon, 2002, p. 118, Formula 28).

When a between-subjects design was used, participants in the experimental TMR group received sensory cues to reactivate prior learning, whereas participants in the control group received learning-incongruent sensory cues or no cues at all (e.g., He et al., 2015; Rihm et al., 2014; Sterpenich et al., 2014). Here, to calculate TMR effect sizes, we preferentially chose the incongruent cue control group over the no-stimulation group to make sensory stimulation constant between groups. The no-stimulation group was used when this was the only control group available, or when there were multiple TMR experiments and thus multiple control groups were needed (as in Sterpenich et al., 2014, when both N2 and REM TMR were examined). For between-subjects TMR studies, we searched for the pre- versus postsleep memory change scores from the experimental and control group and their associated *SD*s. The change scores and the associated *SD*s for experimental and control groups were used to calculate effect size in terms of Cohen's *d*s (Lakens, 2013, Formula 1). When means and *SD*s/*SE*s were not reported in the article, we again searched for key statistical tests that examined TMR effects. Here, the effect could be tested in a mixed 2 (between-subjects variable: TMR vs. control groups) × 2 (within-subject variable, pre- vs. postsleep) *ANOVA*. Alternatively, the TMR effect could be derived from an independent sample *t* test comparing postsleep memory performance between the experimental and control groups, or comparing pre- versus postsleep memory change scores between the two groups. We then transformed the *F* and the *t* values from these statistical tests to calculate effect sizes in Cohen's *d*s (Lakens, 2013, Formula 2; Morris & DeShon, 2002, p. 118, Formula 27).

Lastly, as effect sizes in Cohen's *d* are upward biased with small samples (Lakens, 2013, p. 5), we employed Hedges' *g* correction function to all individual effect sizes: Hedges' g = Cohen's $d \times (1 - [3/[4 \times df - 1]])$, where *df* denotes degree of freedom reported in the statistical test (Hedges, 1981, see also Borenstein et al., 2011; Formula 4.22).

Publication Bias Analyses

We employed a variety of methods to investigate how publication bias may influence the estimated effect sizes from sleep TMR research. We first used a funnel plot to display effect sizes against their standard errors. According to Egger, Davey Smith, Schneider, and Minder (1997), existence of publication bias can be detected through an asymmetric funnel plot because low-powered

positive findings are more likely to be published than equally powered negative findings.

Second, we employed the trim-fill method (Duval & Tweedie, 2000), which imputes artificial effect sizes to make the funnel plot symmetric, and then calculated corrected effect sizes. Third, we used publication status (published vs. unpublished) as a categorical moderator to assess whether published studies have significantly larger effect sizes than unpublished studies.

Fourth, we chose the three-parameter likelihood selection model (Iyengar & Greenhouse, 1988), which extends the original selection model proposed by Hedges (1984) in estimating and correcting publication bias. The three-parameter model includes not only the synthesized effect size as a parameter, but also considers the heterogeneity across effect sizes, and the probability of nonsignificant studies to be published calculated by the maximum likelihood function. In the current study, the three-parameter selection model was set as a one-tailed model with the probability of publishing nonsignificant studies with a step function cut-off at $p = .025$ by maximum likelihood, following the assumption that directionally consistent and statistically significant studies are more likely to be published. Notably, this three-parameter selection model shows promising performance to adjust effect size in conditions varying in the synthesized effect size, heterogeneity, sample size, and the extent of publication bias across different simulation studies (Carter, Schönbrodt, Gervais, & Hilgard, 2019; McShane, Böckenholt, & Hansen, 2016).

Fifth, we employed a selection model with a priori weight functions that could model four different scenarios of publication biases: moderate one-tailed selection, severe one-tailed selection, moderate two-tailed selection, and severe two-tailed selection (Vevea & Woods, 2005). This analysis is advantageous because it shows how estimated effect size may change based on the different magnitudes of publication biases. The specification of priori weights follows the implementation of Vevea and Woods (2005).

Meta-Analytic Procedure

We chose a three-level random-effects model over a fixed-effects model. This choice of model is based on the following reasoning.

First, TMR research is characterized by experimental procedures with particular memory tasks administered in conjunction with TMR during different sleep stages. Therefore, we expected considerable heterogeneity across studies.

Second, a random-effects model assumes heterogeneity due to systematic variance among studies, above and beyond sampling error. A random-effects model will thus generate larger standard errors than fixed-effects models, which will lead to more conservative findings and reduced false positives in both overall effect-size estimates and moderator analyses.

Third and most importantly, many TMR experiments have reported more than one measure of memory performance, which violates the key assumption of data independence in typical random-effect models (Borenstein et al., 2011; Lipsey & Wilson, 2001). As an extension of the random-effects model, multilevel meta-analyses can model both within- and between-study variance and thus can address the issue of dependencies (Van den Noortgate & Onghena, 2003). In short, we employed the multilevel meta-analytical approach to model three levels of variance: (a) variances due to sampling error, (b) within-study variances among multiple effect sizes from the same experiment, and (c) between-study variances among different experiments.

Meta-Analytical Computation

Individual effect sizes and corresponding variance measures at an outcome level were calculated in the Comprehensive Meta-Analysis Software Version 3.3.070 (Biostate, Englewood, NJ) in Hedges' g. These values were then fed into the multilevel model using R package "metaphor" (Viechtbauer, 2010). To examine how much effect sizes varied from each other in the multilevel model, we used Cochran's Q statistic to test whether individual effect size would vary significantly across the whole dataset (i.e., heterogeneity, Borenstein et al., 2011; Cheung, 2014). A significant Q statistic indicates significant heterogeneity across studies that cannot be explained by sampling error. We report between-studies I^2 that denotes that among observed variance across the whole dataset, how much variance in proportional terms is due to differences in true effect sizes between studies rather than sampling error (Higgins & Thompson, 2002). We report τ^2 that denotes the variance of estimated effect sizes at an experiment level, while τ indicates standard deviation.

Results

The search and selection process of applicable data sets are shown in the Figure 2 PRISMA flowchart. Included articles can be found in the reference section and are marked with asterisks. Sample and experimental characteristics of included experiments are shown in Table 1, with corresponding effect sizes provided in both Table 1 and Figure 3. All study information and the associated effect size at an outcome level are available in online supplementary material. All data and analysis code can be found in https://osf.io/kg8y3/?view_only=bfffc7cef5d848afbcf795769d6a7112.

Study and Sample Characteristics

We collected 73 articles/abstracts/data sets, which contain $n = 91$ experiments with 111 independent samples. The total number of participants was 2,004. This dataset contributed $k = 212$ effect sizes to the meta-analysis, with each experiment contributing 2.33 effect sizes on average. Across the whole dataset, the mean sample size for each experiment was 22, with an average age of 23-years-old. The mean age within single experiments ranged from 13- to 71-year-old populations, thus covering adolescent, adult, and aging populations. Of these experiments, 51 were conducted in Europe, 31 in North America, five in Asia, and one in South America. Neither age ($\beta = -0.003$, 95% CI [−0.020, 0.015], $p = .747$) nor female:male ratio ($\beta = -0.443$, 95% CI [−0.940, 0.055], $p = .081$) had a significant impact on TMR effects.

Overall Sleep TMR Effects and Publication Bias Analyses

Across all TMR sleep experiments/conditions, sleep TMR showed a significant effect influencing learning with Hedges' $g = 0.29$, 95% CI [0.21, 0.38], $Z = 6.711$, $p < .001$. Despite this significant TMR effect, there was considerable heterogeneity

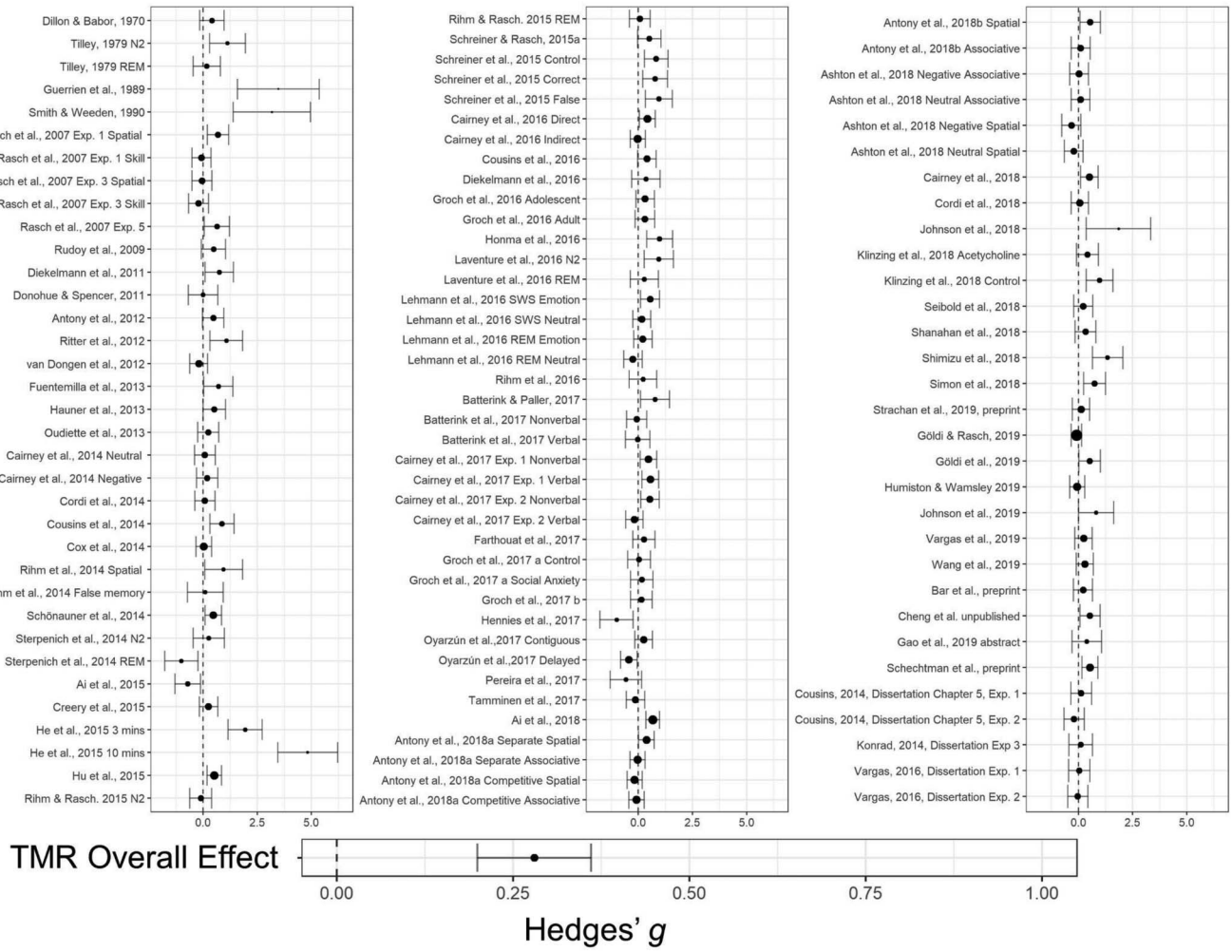

Figure 3. A forest plot displaying sleep Targeted memory reactivation (TMR) effect sizes calculated from each experiment at a task level, matching descriptive from Table 1. The overall TMR effect was presented, calculated from a random effects model using task-level effect sizes from the forest plot and Table 1.

across effect sizes as revealed by heterogeneity analysis, $Q(211) = 588$, $I^2 = 71\%$, $p < .001$, with $\tau^2 = 0.112$ at an experimental level (i.e., between-experiment, Level 3) and $\tau^2 = 0.031$ at an outcome level (i.e., within-experiment, Level 2). This heterogeneity across studies, and the finding that 71% of variances reflects true differences across effect sizes instead of sampling errors, strongly suggests that TMR effects must be compared across experimental conditions.

Regarding publication biases, Egger's test showed that the funnel-plot was significantly asymmetric, $Z = 8.489$, $p < .001$, indicating the existence of publication biases (see Figure 4). With the trim and fill method, 17 artificial effect sizes were imputed to adjust for potential biases. For the overall sleep TMR effect, the adjusted effect size was still significantly above zero, Hedges' $g = 0.18$, 95% CI [0.06, 0.30], $Z = 2.944$, $p = .003$.

When publication status (yes vs. no) was examined in the moderator analysis, we found that publication status did not significantly influence effect sizes $Q(1) = 1.005$, $p = .316$, with unpublished studies ($k = 26$) associated with a positive yet non-significant effect size, Hedges' $g = 0.18$, 95% CI [−0.06, 0.42], $Z = 1.447$, $p = .148$, while published studies ($k = 186$) had a significant effect size, Hedges' $g = 0.31$, 95% CI [0.22, 0.41], $Z = 6.563$, $p < .001$.

Results from the three-parameter selection model again showed a significant adjusted effect size, with Hedges' $g = 0.13$, 95% CI [0.06, 0.21], $Z = 3.472$, $p < .001$. Lastly, employing the selection models with a priori weight functions to model different magnitudes of publication selection processes (Vevea & Woods, 2005), we found that sleep TMR appeared smaller, but remained significant under various scenarios of publication biases: Hedges' $g = 0.21$ for moderate two-tailed selection; $g = 0.17$ for severe two-tailed selection; $g = 0.15$ moderate one-tailed selection, except in the severe one-tailed selection: $g = -0.05$.

Moderator Analyses

Because moderator and focal analyses will have fewer effect sizes available, potential outliers and influential cases may signif-

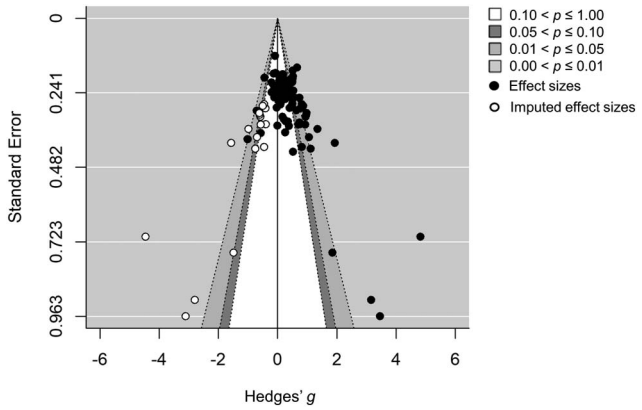

Figure 4. A contour-enhanced funnel plot displaying all effect sizes at experiment levels (solid circles) from sleep TMR research. Y-axis indicates standard errors of effect sizes, x-axis indicates magnitudes of effect sizes in terms of Hedges' g. Imputed effect sizes calculated from the Trim-and-Fill analysis are displayed in open circles.

icantly influence results. We thus excluded data designated as statistical outliers (studentized residuals smaller or larger than three, $k = 4$, with two from SWS TMRs and two from REM TMRs, with all outliers' studentized residuals larger than three, i.e., significantly larger TMR effects). We then conducted influential case analyses to identify effect sizes that exert considerable influence on the analyses (see Viechtbauer & Cheung, 2010). Influential cases ($k = 2$) matched those designated as statistical outliers. This left 208 effect sizes in the sleep TMR analysis. In wake TMR, two influential cases were identified and were excluded from the subsequent analyses. Outliers and influential case analyses can be found in online supplementary material.

TMR cueing stage. Our first question concerns whether the TMR effect was specific to certain cueing stages. As described in the Method section (see also Table 1), we coded TMR cueing stages into five categorical moderators: N2 ($k = 13$), SWS ($k = 174$), REM ($k = 15$), unspecified ($k = 6$), and wake ($k = 30$). Results show that cueing stage had a significant influence on TMR effects, $Q(4) = 10.744$, $p = .03$. Specifically, TMR was only significant during the two NREM stages: N2 and SWS. In contrast, TMR was ineffective when cueing was administered during REM, or when TMR was not supervised by EEG monitoring, or during wakefulness (see Table 2, Figure 5a).

Sleep duration. We then coded sleep duration as a continuous variable, ranging from 0.67-hr nap to 8-hr overnight sleep. We entered sleep duration as a predictor, with TMR effect as the dependent variable in a metaregression model. Results showed that sleep duration did not significantly influence TMR effects, $\beta = 0.003$, 95% CI [−0.022, 0.028], $p = .795$ (see Figure 6).

In the following moderator analyses, we further excluded (a) unspecified TMR experiments because procedurally, this line of research deviates significantly from other TMR experiments during which sleep is monitored by EEGs ($k = 6$, Dillon & Babor, 1970; Donohue & Spencer, 2011; Göldi & Rasch, 2019; Ritter et al., 2012); and (b) one tactile stimulation TMR study ($k = 2$, Pereira et al., 2017) because it is the only tactile TMR study available, which limits conclusions concerning comparisons with other TMR studies.

Learning types. Following current theories regarding memory systems, we categorized learning tasks into four categories: declarative memory ($k = 153$), skill learning ($k = 25$), conditioning ($k = 10$), and the other types of learning ($k = 12$). Descriptions of memory tasks and their assigned categories can be found in Table 1. Results showed that TMR effects varied significantly among different learning types; $Q(3) = 8.056$, $p = .045$. Specifically, TMR influenced all types of learning except for conditioning (see Table 3, Figure 5b).

Outcome measurements. Based on how TMR research measured behavioral outcomes, we categorized each outcome into the following categories: recall ($k = 103$), recognition ($k = 14$), performance ($k = 46$), SCR ($k = 4$), and subjective ratings ($k = 33$). Specific outcomes and their assigned categories can be found in the online supplementary material. Results showed that TMR effects varied significantly depending on how outcomes were assessed, $Q(4) = 11.132$, $p = .025$. Specifically, TMR had a significant effect on recall and performance measurements, while it had a nonsignificant effect on recognition, SCR, and subjective ratings (see Table 3, Figure 5c).

TMR design. There was no significant difference between these two types of design, $Q(1) = 0.055$, $p = .814$. Both between- and within-subject designs were associated with significant and highly comparable TMR effects (see Table 4, Figure 5d).

Cueing modality. All three TMR cueing modalities—auditory_nonverbal, auditory_verbal, and olfactory cues—were associated with significant and comparable TMR effects: $Q(2) = 0.688$, $p = .709$ (see Table 4, Figure 5e).

Table 2
Statistics From Cueing Stages Moderator Analyses

Moderators	*n*(*N*)	*k*	Hedges' *g*	95% CI	Q_B	*Z*	*p*
Cueing stages					10.744		.030
N2	6 (165)	13	.32	[.04, .60]		2.232	.026
SWS	70 (1471)	174	.27	[.20, .35]		6.934	<.001
REM	7 (142)	15	−.06	[−.31, .18]		−.501	.616
Unspecified	4 (140)	6	.26	[−.11, .62]		1.383	.167
Wake	18 (366)	30	.07	[−.09, .23]		.853	.394

Note. REM = rapid eye movement; SWS = slow-wave sleep; *n* = number of experiments/datasets; *N* = number of participants; *k* = number of effect sizes.

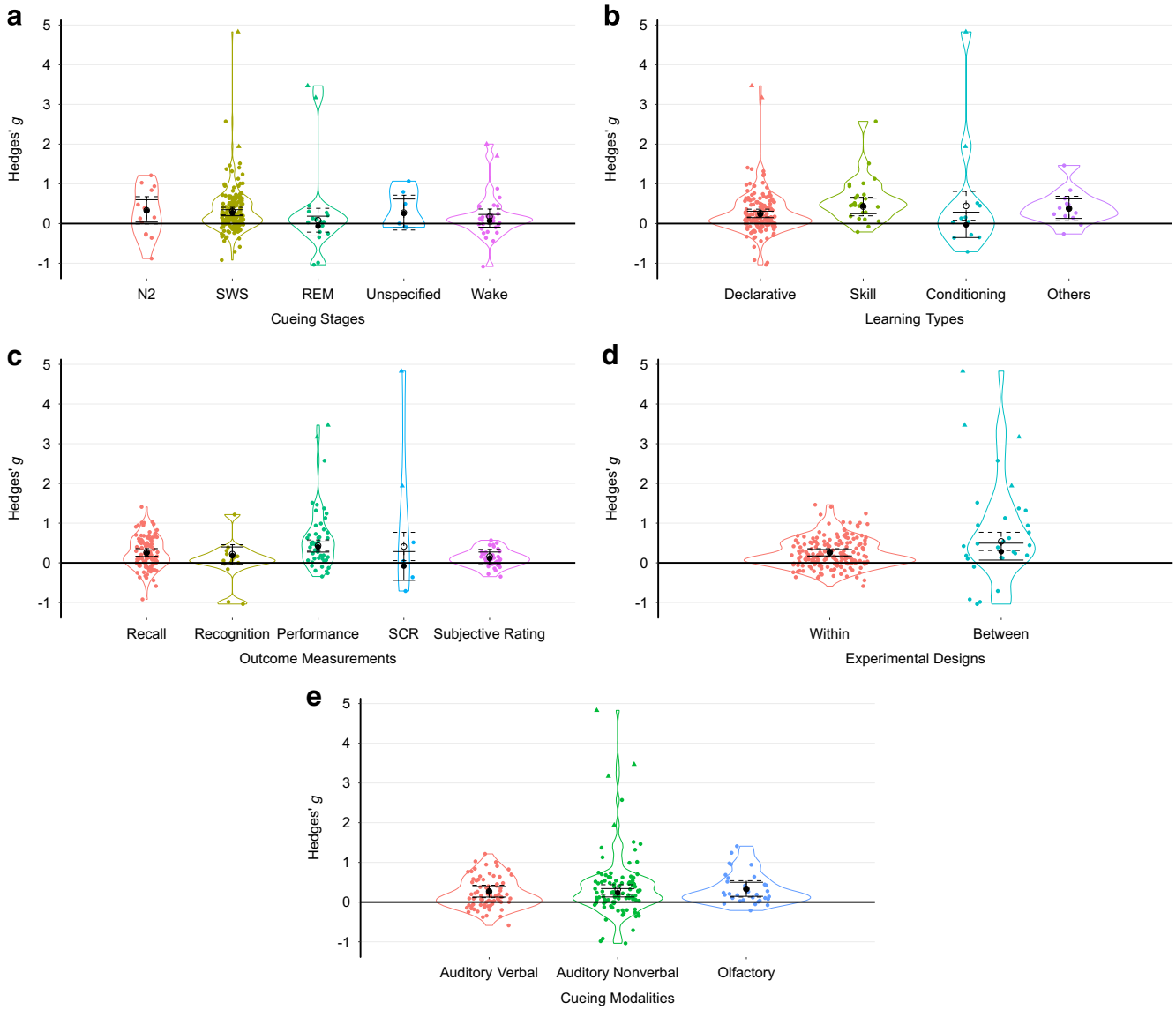

Figure 5. Results of moderator analyses from (a) cueing stages; (b) learning types; (c) outcome measurements; (d) experimental designs and (e) cueing modalities. Each data point represents an individual effect size at an outcome level. Statistical outliers are the same as those indicated in Table 1 and are marked as triangles. The figure displays aggregated effect sizes from each moderator analyses, with error bars representing 95% CIs. The figure displays both results without outliers (solid lines with solid circles) and results including all data points (dashed lines with open circles). N = number of participants; SWS = slow-wave sleep; REM = rapid-eye-movement; SCR = skin conductance response. See the online article for the color version of this figure.

Focal Analyses

In this section, we present a set of analyses that segregated subsets of relatively homogenous TMR studies in terms of sleep cueing stages and memory tasks. Because only N2 and SWS TMR effects were significant, we combined these experiments as NREM TMR (note that the two outliers from NREM TMR and the tactile N2 TMR study was not included in focal analyses). Focal analyses includes the following categories: spatial learning (k = 43), associative learning (k = 30), language acquisition (k = 13), false memories (k = 7), skill learning (k = 23), cognitive bias modification (k = 36), emotional memories (k = 12), and fearful memories (k = 4). Results are displayed in Figure 7. Studies included can be found in Table 1, with effect sizes at an outcome level reported in online supplementary material. We present these analyses in a descriptive manner rather than making strong conclusions.

Spatial memories. In spatial learning tasks, participants learned spatial locations of objects on a two-dimensional grid and practiced placing the objects on the grid followed by feedback (e.g., Rasch et al., 2007; Rudoy et al., 2009). We identified 26

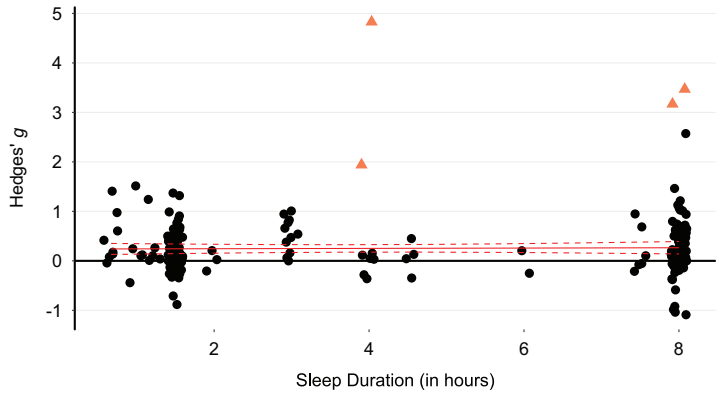

Figure 6. A meta-regression analysis revealed no relationship between sleep length and TMR effects. Statistical outliers are the same as those indicated in Table 1 and are marked as triangles. The regression line (the solid line) and its 95% confidence intervals (the dashed lines) were calculated from the meta-regression model without outliers. See the online article for the color version of this figure.

experiments and 43 effect sizes. For this category, TMR during NREM significantly enhanced spatial memories, Hedges' g = 0.30, 95% CI [0.17, 0.44], Z = 4.439, p < .001 (see Table 5, Figure 7a).

Associative learning. Associative learning tasks involve learning associations between two stimuli (e.g., word/sound–word/picture pairings). Participants memorized associations between two stimuli and then attempted to recall the second member of a pair given the first (Cairney et al., 2018; Fuentemilla et al., 2013). We found that TMR during NREM sleep significantly improved associative learning in these tasks, Hedges' g = 0.17, 95% CI [0.03, 0.30], Z = 2.354, p = .019 (see Table 5, Figure 7a).

Language acquisition. This analysis included two lines of research. For vocabulary acquisition, participants memorized novel words (e.g., from a second language) that were paired with words from participants' native language. During sleep, the second-language words were presented to reactivate the associated memories (e.g., Batterink et al., 2017; Cordi et al., 2018; Schreiner & Rasch, 2015a; Schreiner et al., 2015). For grammatical learning and generalization, participants extracted grammatical regularities by learning nonword sequences based on feedback (Batterink & Paller, 2017). Eight experiments reported nine effect sizes, and results suggest that TMR can significantly promote language acquisition in these circumstances, Hedges' g = 0.40, 95% CI [0.14, 0.65], Z = 3.046, p = .002 (see Table 5, Figure 7a).

False memories. For this category, TMR was used during sleep to determine whether cues could enhance false memories. We identified four experiments that examined this type of question (Rihm et al., 2014, unpublished dataset; Cousins, 2014, unpublished dissertation, Chapter 5, Experiments 1 and 2; Vargas, 2016, unpublished dissertation, Experiment 1). None of the single studies found a significant impact of TMR on false memories. Overall, TMR failed to influence false memories during sleep, Hedges' g = −0.01, 95% CI [−0.20, 0.18], Z = −0.103, p = .918 (see Table 5, Figure 7a).

Skill learning. Studies typically included in the skill-learning category are included in this analysis. We focused on measures that sometimes are indicative of implicit performance, namely speed and accuracy, but the range of designs used does not permit any general claims about whether learning was implicit or explicit. Generally, a positive TMR effect would indicate faster or more accurate performance in a motor task.

Table 3
Statistics From Learning and Outcome Measurements Moderator Analyses

Moderators	$n(N)$	k	Hedges' g	95% CI	Q_B	Z	p
Learning type					8.056		.045
Declarative	62 (1219)	153	.23	[.15, .31]		5.563	<.001
Skill	12 (283)	25	.44	[.25, .64]		4.438	<.001
Conditioning	4 (91)	10	−.03	[−.35, .29]		−.200	.841
Others	6 (191)	12	.38	[.13, .62]		2.991	.003
Outcome measurements					11.132		.025
Recall	61 (1137)	103	.24	[.16, .33]		5.676	<.001
Recognition	9 (157)	14	.18	[−.04, .40]		1.619	.105
Performance	27 (673)	46	.40	[.27, .53]		6.103	<.001
SCR	4 (91)	4	−.08	[−.44, .28]		−.423	.672
Subjective rating	8 (135)	33	.11	[−.05, .27]		1.355	.175

Note. SCR = skin conductance response; n = number of experiments/datasets; N = number of participants; k = number of effect sizes.

Table 4
Statistics From Experimental Designs and Cueing Modalities Moderator Analyses

Moderators	*n*(*N*)	*k*	Hedges' *g*	95% CI	Q_B	*Z*	*p*
Experimental design					.055		.814
Within	68 (1303)	173	.25	[.17, .34]		6.192	<.001
Between	14 (446)	27	.28	[.07, .50]		2.595	.009
Cueing modality					.688		.709
Auditory_verbal	25 (472)	74	.26	[.13, .39]		3.825	<.001
Auditory_nonverbal	42 (956)	94	.23	[.13, .34]		4.365	<.001
Olfactory	17 (372)	32	.32	[.15, .50]		3.566	<.001

Note. *n* = number of experiments/datasets; *N* = number of participants; *k* = number of effect sizes.

With 18 effect sizes, TMR during NREM enhanced motor performance with a Hedges' $g = 0.54$, 95% CI [0.38, 0.69], $Z = 6.782$, $p < .001$. For comparison purposes, we also analyzed TMR's impact on explicit knowledge of skill learning as assessed by explicit memory of motor sequence. With five effect sizes, TMR significantly improved conscious recall of motor sequences with a Hedges' $g = 0.41$, 95% CI [0.04, 0.78], $Z = 2.156$, $p = .031$ (see Table 5, Figure 7b).

Cognitive bias modifications. Employing a picture–word learning task in which words could be used to disambiguate interpretation of an ambiguous picture, Groch et al. (2016) investigated whether memories of positive or negative words could be reactivated during sleep, aiming to change interpretations of the ambiguous scenes. This procedure has been used in adolescents and adults, those who are healthy, and those with social anxiety (Groch et al., 2016; Groch, Preiss et al., 2017). With 36 effect sizes, we found that TMR during NREM significantly changed participants' memory biases with Hedges' $g = 0.18$, 95% CI [0.06, 0.31], $Z = 2.832$, $p = .005$ (see Table 5, Figure 7b).

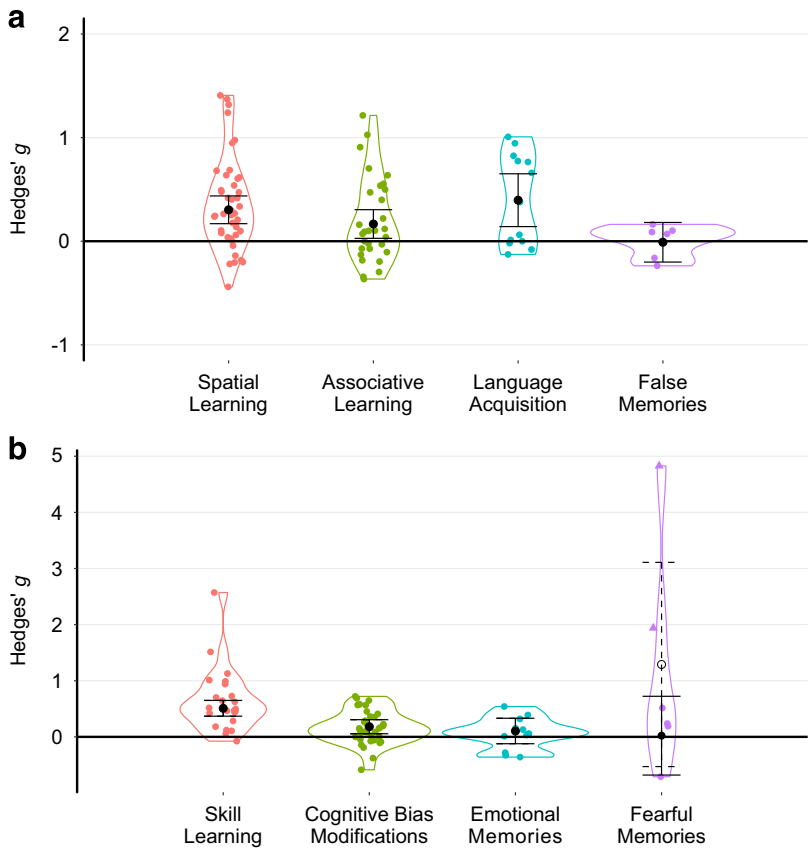

Figure 7. Results of focal analyses. Each data point represents an individual effect size at an outcome level. Statistical outliers are the same as those indicated in Table 1 and are marked as triangles. The figure displays aggregated effect sizes based on each focal analysis, with error bars representing 95% CIs. For fearful memories, the figure displays both result without outliers (the solid line with a solid circle) and result including all data points (the dashed line with an open circle). See the online article for the color version of this figure.

Table 5
Statistics From Focal Analyses

Focal analyses	*n(N)*	*k*	Hedges' *g*	95% CI	*Z*	*p*
Spatial learning	26 (553)	43	.30	[.17, .44]	4.439	<.001
Associative learning	16 (320)	30	.17	[.03, .30]	2.354	.019
Language acquisition	9 (158)	13	.40	[.14, .65]	3.046	.002
False memories	4 (66)	7	−.01	[−.20, .18]	−.103	.918
Skill learning	10 (229)	23	.51	[.37, .65]	7.108	<.001
Cognitive bias modification	4 (66)	36	.18	[.06, .31]	2.832	.005
Emotional memories	5 (97)	12	.10	[−.12, .33]	.905	.366
Fearful memories	3 (97)	4	.02	[−.68, .72]	.059	.953

Note. n = number of experiments/datasets; N = number of participants; k = number of effect sizes.

Emotional memories. TMR has been used to influence consolidation of emotional memories in both associative learning and spatial learning paradigms. In the current analyses, we did not find an overall effect of TMR on emotional memories: Hedges' g = 0.10, 95% CI [−0.12, 0.33], Z = 0.905, p = .366 (see Table 5, Figure 7b).

Fearful memories. Researchers have employed TMR to modulate fear memories during NREM sleep. For example, TMR was applied to aid in fear extinction (Ai et al., 2015; Hauner et al., 2013) and exposure therapy for phobia (Rihm et al., 2016). In the current analyses, TMR did not induce fear extinction during sleep: Hedges' g = 0.02, 95% CI [−0.68, 0.72], Z = 0.059, p = .953 (see Table 5, Figure 7b). Given that sleep could potentially influence fear learning either by strengthening associations or enhancing extinction, we also ran an analysis considering TMR effects irrespective of directions. Results showed that TMR significantly modulates fearful memories (Hedges' g = 0.44, Z = 2.911, p = .004).

Discussion

Forming enduring memories may depend critically on brain mechanisms whereby learned information is spontaneously reactivated, such as during subsequent sleep (Paller et al., 2020). Although spontaneous memory reactivation has been indirectly observed during human sleep (e.g., Deuker et al., 2013; Peigneux et al., 2004), methods to directly manipulate this reactivation should be utilized to promote further understanding, both in human and nonhuman experiments. The method of TMR, by altering memory processing during sleep, may not only advance our understanding of sleep-based memory consolidation, but may also bear significant translational implications for enhancing various types of learning. For the first time, by collecting a comprehensive dataset of studies and conducting a multilevel random-effects meta-analysis, we have provided an overall assessment of TMR's effectiveness. In addition, because this dataset comprised studies using a variety of experimental manipulations, we were able to provide additional information by evaluating the influence of factors such as sleep cueing stages and learning types.

TMR Effect as a Function of Sleep Stage

First, sleep TMR was effective in influencing learning and was associated with a small-to-moderate effect size: Hedges' g = 0.29. TMR effects are likely not the same in sleep versus wake, as effect sizes from N2 and SWS TMR studies were significantly larger than those from REM and wake TMR studies. On the other hand, there are some reports of significant findings from REM and wake TMR (e.g., Oudiette, Antony, Creery, & Paller, 2013 wake TMR group; Sterpenich et al., 2014, REM TMR group). Given the small number of these studies, additional research is likely to produce modified conclusions with respect to TMR during these two conditions.

Because a meta-analysis aggregates multiple TMR studies, we can investigate questions that would be difficult for a single study to address, such as whether sleep duration may differentially influence TMR effects. We found that sleep duration did not influence TMR effects; TMR benefits memory with cues presented during either afternoon or nocturnal NREM. Some have theorized that SWS followed by REM is helpful (see Batterink et al., 2017; Tamminen, Lambon Ralph, & Lewis, 2017), but further data are needed to substantiate this idea.

Because our primary research question concerns TMR during sleep, wake TMR conditions in the present analysis were selected from the identified sleep TMR studies, and they were typically matched with sleep TMR in experimental design features such as timing of cueing and time of testing. It should be noted that only a tiny proportion of the huge number of possible wake conditions have been studied: participants in wake TMR could concurrently perform a working memory task, read a book, watch a movie, rest while mind-wandering, or engage in numerous other activities during wakeful cueing periods. Furthermore, cueing could be followed by new interfering information, as in reconsolidation research that also involves memory reactivation (Forcato, Fernandez, & Pedreira, 2014; Nader & Hardt, 2009; Nader, Schafe, & Le Doux, 2000; Schiller et al., 2010). Another complication is to account for different types of memory that have been emphasized in such studies, from simple conditioning to complex episodic memory paradigms. All these factors pose challenges in generalizing about wake TMR results. In short, given that different experimental procedures with wake TMR can influence memory results (e.g., Tambini et al., 2017), it would be inappropriate to generalize from the small number of wake TMR findings included in this meta-analysis.

TMR's Impact on Learning

Sleep has been implicated in many types of learning and memory, within both the declarative and nondeclarative categories (Korman et al., 2007; Plihal & Born, 1997, for comprehensive reviews see Diekelmann & Born, 2010; Rasch & Born, 2013;

Stickgold & Walker, 2013). Accordingly, it may not be surprising that TMR during sleep can also influence multiple types of learning. However, individual studies varied greatly and many studies reported null or contradictory findings. For example, TMR failed to have a positive impact on sequential finger tapping when olfactory cues were applied during SWS or REM sleep (Rasch et al., 2007). In contrast with these results, subsequent studies found that reactivating motor learning using auditory cues during N2 or SWS could improve performance (Antony et al., 2012; Cousins et al., 2014; Cousins et al., 2016; Laventure et al., 2016; Schönauer et al., 2014). Importantly, different tasks were examined in these different studies, and further work is needed to clarify the relevance of various task factors.

By synthesizing available evidence from different learning tasks, the current meta-analysis shows that TMR can be effective across many types of learning including tasks of declarative memory, skill learning, other types of learning, but not with conditioning. The present meta-analysis also showed that TMR effects depend on how memories are assessed: TMR effects were significant in recall and performance measures, but appeared less effective using recognition, SCR, and subjective ratings. Subsequent focal analyses showed that TMR during NREM significantly influenced associative learning, spatial memories, language acquisition, cognitive bias modification, and skill learning. In contrast, TMR has not had a clear influence on false memories. In the current dataset, the Deese-Roediger-McDermott and reality-monitoring paradigms were used to induce false memories. Both paradigms are well-established in inducing false memories during wakefulness (Gallo, 2010; Gonsalves & Paller, 2000; Gonsalves et al., 2004). However, the role of sleep in influencing false memories remains unclear, as sleep either enhanced or reduced false memories, with effects moderated by presleep encoding quality and retrieval task (e.g., recognition vs. recall, Diekelmann, Landolt, Lahl, Born, & Wagner, 2008; Fenn, Gallo, Margoliash, Roediger, & Nusbaum, 2009; Pardilla-Delgado & Payne, 2017; Payne et al., 2009). By reactivating learning episodes during NREM, TMR might be expected to provide some clarification on this question. However, the experiments we included in the meta-analysis failed to further influence false memories during sleep.

The apparent inability of TMR to trigger false memory reactivation may be related to an emphasis on SWS. Previous reports suggested that SWS may play a detrimental role in the formation of false memories (Pardilla-Delgado & Payne, 2017; Payne et al., 2009), but on the other hand, Vargas (2016, Experiment 1) found a positive correlation between time in SWS and false memory performance. Whether false memories can be modulated by TMR during REM is currently unknown.

Notably, one recent study used TMR to alter memories to reverse prior learning (Simon, Gómez, & Nadel, 2018), which is in some ways akin to a false memory. A tone associated with forgetting was presented during sleep in conjunction with other sounds such that the associated object memories were weakened. In this way, TMR can be used to induce forgetting for specific memories formed previously.

TMR has also been used to enhance the rubber-hand illusion (Honma et al., 2016), whereby subjective ownership and proprioceptive drift of a rubber hand was impacted, likely via the integration of multisensory information. This phenomenon is similar to a false memory in the sense that both are illusory. In this case, integration between visual input of the rubber hand and tactile input to participants' real hand was influenced by TMR during sleep.

Methodological Implications, Statistical Power, and Publication Bias

The TMR methodology provides several advantages for understanding sleep-based memory consolidation. For example, previous research on sleep and memory emphasized comparisons between sleep and wakeful retention intervals to draw inferences about sleep's influence. The waking condition could consist of an ordinary period of wakefulness or a night of total sleep deprivation. In either case, the waking condition does not provide an ideal contrast for the sleep condition because the two conditions can differ in circadian rhythms, sleep drive, and pre-/postencoding interference (e.g., Pan & Rickard, 2015). In contrast, TMR's key experimental manipulation occurs during a specific sleep stage while all other factors are held constant across cued and uncued conditions, including circadian influences and amount of pre- and postencoding interference.

Furthermore, TMR can be advantageous in terms of statistical power given that memory reactivation can be manipulated during a single sleep session on a within-subject basis. Here, we presented analyses regarding experimental design and cueing modality factors. Regarding between- and within-subject designs, our meta-analysis revealed that both designs were associated with comparable effect sizes in influencing memory with TMR. On average, a between-subjects design study would recruit 30 participants, whereas a within-subject design study would recruit 20 participants. This difference in sample size is in keeping with the general rule that within-subject designs provide greater statistical power than do between-subjects designs.

Regarding cueing modality, we categorized stimulation into three types: auditory_nonverbal, auditory_verbal, and olfactory. Consistent with individual reports in which verbal and nonverbal cues were directly compared (e.g., Batterink et al., 2017; Cairney et al., 2017), cues from all modalities could impact learning. Interestingly, nonverbal and verbal cues tend to have the similar effect sizes: 0.26 versus 0.23. The use of verbal cues may greatly expand TMR's applicability in future studies.

Despite robust sleep TMR benefits across different memory types and experimental paradigms, inspection of the full dataset revealed that more than half of the reported results did not reach statistical significance at the conventional .05 false-positive rate: 72 of 212 sleep TMR effect sizes were significant based on Hedges' g and the associated 95% CIs. When constraining analyses to NREM TMR studies, 68 out of 189 effect sizes were significant. Given significant TMR effects for sleep and NREM conditions, and in moderator analyses, null results from individual studies can best be attributed to either moderator choices (e.g., cueing during REM, or when recognition or subjective rating was used) or low statistical power in single studies. In order for evidence to accumulate and guide future research effectively, we recommend that studies be designed with relatively high statistical power based on results provided in the current meta-analysis.

Publication bias can arise when significant findings consistent with researchers' hypotheses are more likely to be published than nonsignificant findings, which poses threats for accurately estimating effect sizes (Rosenthal, 1979). In addition to our efforts to include unpublished data sets, we employed a variety of publication bias adjustment analyses (trim and fill, three-parameter selection model, and the a priori weight functions model) to evaluate the possibility of overestimated effect sizes. Adjusted effect sizes across these analyses remained significant, except for the most extreme case (i.e., the severe, one-tailed selection model). These results, when evaluated holistically, suggest that sleep TMR effects are robust against publication biases. However, as recent simulation studies on publication-bias analyses suggested (Carter et al., 2019; McShane et al., 2016), each analysis has limitations and relies on some assumptions. Given significant heterogeneity across effect sizes and the typical sample sizes involved in TMR research, we urge a continued evaluation of possible publication bias. Moreover, to accurately assess TMR in the future, high statistical power and preregistration strategies are recommended. Lastly, all members of a scientific community, including researchers, reviewers, and journal editors, could work together to combat publication biases by encouraging publication of relevant nonsignificant findings.

Practical Implications

An intriguing possibility for sleep TMR is to complement wakeful learning to enhance cognition and performance (Diekelmann, 2014; Paller, 2017). Among the TMR studies reviewed here, a few topics bear high translational implications in educational and clinical settings. Boosting language acquisition can be particularly meaningful in educational settings. Our dataset included two different types of language studies: vocabulary learning (Batterink et al., 2017; Göldi & Rasch, 2019; Schreiner & Rasch, 2015a; Schreiner et al., 2015) and grammatical learning (Batterink & Paller, 2017). In vocabulary learning, participants associated a foreign or a novel word with its translation in the participants' native language. Newly learned words were subsequently replayed during sleep to reactive their associated meanings. In grammatical learning, participants viewed nonsense phrases and gradually acquired the underlying grammatical rules via trial-and-error. Generalization was assessed when participants were required to generate correct sequences with new nonsense words (Batterink & Paller, 2017). Overall, TMR during NREM sleep boosted language acquisition, with an effect size of 0.40. Future research could include different age groups, such as young children who are just beginning to gain competence in their native language and sleep a lot.

TMR's effectiveness in facilitating skill learning has intriguing implications for motor rehabilitation. Individual studies reported that TMR could enhance participants' speed and/or accuracy (Antony et al., 2012; Laventure et al., 2016), with explicit knowledge of motor sequences in some cases (Cousins et al., 2014; Diekelmann et al., 2016). Importantly, when all effect sizes were considered in the meta-analysis, TMR appeared effective in influencing both performance and knowledge of the learned motor sequences. Future studies can test TMR's potential for facilitating motor or cognitive rehabilitation among patient populations in clinical settings.

TMR may also hold promise for complementing psychotherapy. In the present meta-analysis, we found that TMR was effective in changing memories with respect to ambiguous scenes (e.g., Groch et al., 2016), but did not influence emotional memories or weaken fearful memories. However, evidence on whether TMR may influence emotional memories and fear extinction was highly mixed (Ai et al., 2015; Ashton et al., 2018; Hauner et al., 2013; He et al., 2015; Lehmann et al., 2016). Results have also been mixed in TMR fear extinction studies in rodents (Barnes & Wilson, 2014; Purple et al., 2017; Rolls et al., 2013). Given the potential clinical relevance, future TMR studies with these types of memory are warranted.

Neural Mechanisms and Theoretical Implications

Investigating TMR-elicited neural activity with EEG and fMRI can help researchers delineate neural mechanisms of memory reactivation and consolidation during sleep. By employing time-frequency analyses to decompose EEG responses, researchers have produced evidence implicating theta rhythms and thalamo-cortical spindle oscillations in memory reactivation and consolidation (e.g., Antony, Piloto, et al., 2018; Belal et al., 2018; Cairney et al., 2018; Cox, Hofman, de Boer, & Talamini, 2014; Farthouat et al., 2017; Groch, Preiss, et al., 2017; Laventure et al., 2016; Schreiner et al., 2018; Schreiner et al., 2015; Wang et al., 2019). In particular, decoding cue-elicited brain activities during both wakeful learning and sleep TMR suggests that TMR involves neural patterns resembling prior, wakeful learning content (Belal et al., 2018; Schreiner et al., 2018; Shanahan et al., 2018;). During sleep, TMR-related neural activity could distinguish between distinctive memory representations at a categorical level, with such activity predicting postsleep memory improvement (Cairney et al., 2018; Wang et al., 2019).

In addition to examining neural activity during sleep (Berkers et al., 2018; Diekelmann, Büchel, Born, & Rasch, 2011; Rasch et al., 2007; Shanahan et al., 2018; van Dongen et al., 2012), researchers also investigated task-related neural activity following sleep TMR. For example, reactivating motor learning during SWS enhanced functional connectivity between caudate nucleus and hippocampus when participants were retested on the motor task (Cousins et al., 2016).

In short, beyond behavioral results obtained from the current meta-analysis, neural results can provide additional evidence that TMR promotes consolidation via reactivating prior learning experiences, as described in the active system consolidation hypothesis (Rasch & Born, 2013). Specifically, during NREM sleep, characterized by cortical slow oscillations and thalamocortical spindles, covert memory reactivation can transform newly acquired, hippocampus-dependent learning such that neocortical representations become more stable and resistant to interference.

More research is needed to understand why memory reactivation during sleep is associated with consolidation. Some intriguing clues about relevant neural mechanisms have been obtained to date. For example, TMR cues were found to be more effective when delivered just after spindle refractory periods (Antony, Piloto et al., 2018), and less effective when cues were presented closely together (Farthouat et al., 2017; Schreiner et al., 2015). Regarding REM's role in memory consolidation, although the present meta-analysis did not find a significant REM TMR effect, it remains

possible that REM may aid consolidation following reactivation during NREM (Batterink et al., 2017; Tamminen et al., 2017), as proposed in the two-stage sequential processing account (Giuditta, 2014). REM sleep may play an important role for specific types of processing, such as with distant associations, information integration, and emotional memories (Cai, Mednick, Harrison, Kanady, & Mednick, 2009; Sterpenich et al., 2014; Tamminen et al., 2017; Wassing et al., 2019). Additional studies are warranted to explore the impact of REM sleep on memory processing.

TMR and Reconsolidation

Wake TMR studies resemble reconsolidation studies as both procedures involve encoding, presentation of memory reminders during wakefulness, and subsequent testing. On the other hand, there are notable differences. First, in wake TMR studies memories are typically reactivated shortly after encoding (e.g., within minutes or hours), whereas reconsolidation paradigms tend to reactivate memories following longer delays. Second, wake TMR studies often aim to test whether reactivation during wakefulness stabilizes memories, whereas reconsolidation designs introduce interfering information to modify original memories (Elsey, Van Ast, & Kindt, 2018; Forcato et al., 2014; Kredlow, Unger, & Otto, 2016; Nader & Hardt, 2009; Nader et al., 2000; Schiller et al., 2010). For both types of studies, it is of course essential to consider whether results vary depending on the type of memory examined (e.g., declarative memory vs. conditioning).

Although reactivation could render memories labile and make them susceptible to interfering information, caution must be exercised before inferring that memories were made labile by the experimental manipulation. This issue may be particularly relevant for declarative memories, which may remain modifiable indefinitely (Dudai, 2012). As a case in point, Diekelmann, Büchel, Born, and Rasch (2011) studied TMR followed by interference and found memory impairment after wake TMR, in contrast to the usual memory strengthening effect after NREM TMR. An alternative interpretation for the memory impairment, however, is that wake TMR in this study functioned to blur the temporal distinctiveness of the original information versus the interference information, as odor presentation bridged the two task periods. If the original and interfering information were less temporally distinct in this condition, poorer memory performance would be expected. Therefore, such results do not necessarily provide support for the idea of converting declarative memories into a labile form or for conventional reconsolidation models. Nevertheless, further integration between TMR and reconsolidation research could deepen our understanding of the mechanisms of memory processing, including reactivation, consolidation, and updating.

Limitations and Ethical Concerns

Meta-analysis provides a powerful tool to quantitatively estimate the strength of experimental manipulations, but results that aggregate and summarize a diverse set of paradigms may not be adequate for guiding specific research questions. To overcome this limitation, in addition to presenting syntheses of TMR effects across all experiments and broadly defined topics, we included focal analyses based on selected homogenous manipulations (e.g., NREM only) and learning topics (e.g., associative learning, spatial learning, false memory). These focal analyses could be valuable for providing effect-size estimates pertaining to specific research questions.

Another limitation relates to the way memory tasks were categorized in the learning-type moderator analyses. Many tasks used in TMR studies could not be unambiguously categorized (e.g., trust learning, counterstereotype learning, multisensory integration, value-based decision making). Furthermore, some tasks placed in one learning category may engage processing that depends on multiple memory systems operative concurrently. For example, artificial grammar learning and other types of statistical learning may involve both implicit learning and declarative memory (e.g., Batterink, Reber, Neville, & Paller, 2015). Some skill learning may engender explicit remembering of motor sequences (i.e., declarative memories) and may engage hippocampal contributions (e.g., Antony et al., 2012; Cousins et al., 2016). It is possible that the combination of explicit and implicit learning of motor sequences makes them more susceptible to memory reactivation during SWS, with corresponding changes in hippocampal-striatal networks (Albouy et al., 2008; Cousins et al., 2016; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). Acknowledging this limitation, we present individual effect size and variance data for currently available TMR studies with which researchers can reanalyze the data based on any categorization.

TMR may be applicable for many beneficial purposes, but can it also be employed maliciously for mind control? Here it is important to distinguish between new learning and prior learning. People may be able to acquire new information while asleep, but perhaps only in restricted circumstances (e.g., Andrillon, Pressnitzer, Léger, & Kouider, 2017; Arzi et al., 2012; Züst et al., 2019). In the case of conditioning during sleep, the idea of introducing new associations without the individual's awareness parallels the idea of subliminal conditioning while awake. Although the term "sleep learning" usually has the connotation of acquiring new information, the typical process of learning that begins during wakefulness may continue during sleep, in which case sleep is indeed relevant for learning. The effectiveness of TMR is generally contingent on prior learning and associations made with specific cue stimuli (Cairney et al., 2016; Creery et al., 2015). When the learning occurs with a person's full knowledge and compliance, concerns about mind control are mitigated. However, variants of TMR could be used in future research to attempt to selectively weaken memories (as in Simon et al., 2018), or to change memories, perhaps to the point of creating a false memory or providing a conditioned association that was not present during waking. We thus advocate for the continuing evaluation of ethical concerns as research in this area continues to expand.

Unanswered Questions and Future Directions

Although our results showed that TMR could significantly modify memory processing during NREM sleep, effect sizes varied across studies and tasks, as evidenced by observed heterogeneity. The overall effect size was small to moderate in Cohen's terms (Cohen, 1988). Thus, one future direction is to investigate how to improve TMR effects. Recent findings indicate that the timing of cue presentation relative to spindles and to the phase of slow oscillations can be critical to the degree of reactivation and consolidation (Antony, Piloto, et al., 2018; Batterink et al., 2016;

Göldi et al., 2019; Shimizu et al., 2018). Thus, a promising research direction will be to test the timing of cueing in relation with slow oscillations and/or spindles via techniques such as closed-loop stimulation.

One intriguing yet unanswered question regards whether targeted and spontaneous memory reactivation entail the same or qualitatively different neural mechanisms. Cueing may simply bias spontaneous reactivation (e.g., Bendor & Wilson, 2012), but there may be important differences. Because neural signals that completely and unequivocally indicate memory reactivation during sleep have not yet been established, this question remains open. Future research could address this question by comparing neural activity associated with targeted versus spontaneous reactivation using various memory paradigms.

Another question about TMR is whether it impacts other learning. That is, if TMR improves memory for cued information, does it harm memory consolidation for information acquired via other recent learning? If some information is reactivated, other information may be less likely to be reactivated. Investigations are limited in that they cannot measure all memories that people recently acquired that might be influenced by TMR. One sense in which memory reactivation can have additional effects is in terms of interrelationships among memories. That is, memory storage may normally involve competition, such that enhanced storage of some information would be expected to have repercussions (Norman, Newman, & Detre, 2007; Paller et al., 2020). In this regard, TMR research has begun to examine how competing memories interact during sleep (Antony, Cheng et al., 2018; Oyarzún et al., 2017), with evidence showing that competition may weaken memories that are tightly interrelated with cued information.

Many other questions remain to be tested in relation to potential applications of TMR outside the laboratory. One recent study investigated TMR for vocabulary learning in a naturalistic home sleep setting (i.e., unsupervised TMR) using auditory cues presented without EEG monitoring (Göldi & Rasch, 2019). TMR benefits were achieved only among participants for whom sleep was not disturbed by the cues. These results underscore the importance of avoiding arousal from sleep for memory improvement to be observed. Finally, whereas lab TMR studies generally include only one period of sleep with TMR, it will be important to determine whether TMR can have cumulative effects across multiple sleep sessions.

Conclusion

To conclude, by aggregating effect sizes across a comprehensive dataset of TMR research, we present the first quantitative synthesis of the effectiveness of TMR under various conditions. Despite some inconsistent results from single studies, meta-analytical results provide compelling evidence that applying sensory cues during NREM sleep can reactivate associated memories and promote memory consolidation. TMR effects are found across a range of learning domains, including but not limited to declarative memory and skill learning. Whether TMR can be meaningfully beneficial in educational and clinical settings can only be answered via future studies in such settings. We hope this review and meta-analysis will facilitate new studies to advance this exciting field.

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