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CLINICAL REVIEW

State of the art on targeted memory reactivation: Sleep your way to enhanced cognition

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SUMMARY

Targeted memory reactivation is a fairly simple technique that has the potential to influence the course of memory formation through application of cues during sleep. Studies have shown that cueing memory during sleep can lead to either an enhanced or decreased representation of the information encoded in the targeted networks, depending on experimental variations. The effects have been associated with sleep parameters and accompanied by activation of memory related brain areas. The findings suggest a causal role of neuronal replay in memory consolidation and provide evidence for the active system consolidation hypothesis. However, the observed inconsistencies across studies suggest that further research is warranted regarding the underlying neural mechanisms and optimal conditions for the application of targeted memory reactivation. The goal of the present review is to integrate the currently available experimental data and to provide an overview of this technique's limitations and pitfalls, as well as its potential applications in everyday use and clinical treatment. Exploring the open questions herein identified should lead to insight into safer and more effective ways of adjusting memory representations to better suit individual needs.

Introduction

Over the last few years, memory researchers have developed promising new ways to track and influence the course of memory evolution. Sleep represents an optimal time window for memory consolidation, as has been extensively discussed in previous publications [1–4] (for a review on sleep and memory definitions, please refer to [5] and [6,7], respectively).

The technique known as 'targeted memory reactivation' (TMR) [8] emerged recently as a promising tool to aid in unraveling the mechanisms of sleep-dependent memory consolidation. TMR is based on evidence showing that hippocampal neuronal networks recruited for encoding new information are spontaneously reactivated during sleep [9–11], thereby strengthening the representations therein stored [11,12]. In a typical TMR protocol, the sleeping brain is exposed to an olfactory [13] or auditory [14] cue present in the context where learning took place. When an engram is cued, it is assumed that neuronal replay is artificially triggered, which most likely benefits memory consolidation through the same mechanisms triggered by spontaneous reactivations. However, a thorough description of how a cue is able to bias the content of hippocampal replay towards its associated material is yet to be put forward.[2]

Abbreviations: NREM, non-rapid eye movement; NREM 2, non-rapid eye movement sleep stage two; REM, rapid eye movement; SHY, synaptic homeostasis hypothesis; SWS, slow wave sleep; TMR, targeted memory reactivation.

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[2] Many studies claim to have elicited 'memory reactivation' through cue presentation, but without direct experimental evidence this is in fact an assumption. There is still no consensus on the actual manner in which memory is consolidated and 'memory reactivation' is but one of the possible explanations (passive protection from interference and synaptic downscaling are two alternatives, among others). In addition, it is the network of neurons representing a given engram that could potentially be subjected to reactivation, not the 'memory' *per se*. Hence, we propose that the term 'targeted memory reactivation', widely used in the literature and also in the present report for consistency, warrants reviewing.

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Glossary of terms

neuronal replay/reactivation: the re-occurrence in an offline period of spatiotemporal activation patterns previously recorded during active wakefulness

cueing/stimulation: the presentation of auditory or olfactory cues during sleep

memory consolidation: the processes through which a memory trace is stabilized and integrated into a network of pre-existing related memories

Table 1
Tasks used to test TMR according to the cognitive domain probed.

Cognitive domain	Task
Declarative memory	2D object-location task [13,15–17,50]
	Sound-picture location association task [14,43,45,47]
	Vocabulary learning task [18,19]
	Sound-picture association task [20]
	Auditory-spatial association task [42]
	Associative word-pair learning [46]
	Odor-word location task [48]
	Sound-word location task [58]
Procedural memory	Finger tapping task [13]
	Modified serial reaction time task [23,26*,27]
Emotional memory	Fear conditioning paradigms [28–32,44]
	Pavlovian odor-tone conditioning [33]
	Picture-location association task [34]
	Modified picture-word association task [36]
Creativity	Unusual uses task [40]
Social cognition	Counterbias training [41]

TMR – targeted memory reactivation; *Although the authors claim to have employed the finger tapping task (explicit learning), it is clear from the task description that in fact a modified version of the serial reaction time task (implicit learning) was performed; Note: consult references for task description.

The present review aims at integrating the available experimental evidence on the effects of TMR on declarative, procedural and emotional memory, as well as creativity and social cognition. The first section provides an overview of the cognitive abilities probed in TMR studies and describes consistent findings as well as the technique's limitations and pitfalls. The following sections will address the influence of variations in the experimental design on the behavioral outcome of TMR and the neural correlates of the technique will be discussed in combination with their relation to present theoretical frameworks. The review will conclude with an outlook on potential applications and guidance on future research directions, since this tool could prove useful for cognitive enhancement and psychotherapy.

The effects of TMR on cognition

The tasks that have been used to test the effect of TMR are summarized in Table 1, grouped according to the cognitive domain probed.

Declarative memory

TMR has been shown to improve declarative memory consolidation in humans as assessed by performance during subsequent retrieval testing [13,15–19]. Through TMR, memories can be strengthened and transformed into a more stable form rendering them more resistant to interfering inputs and less vulnerable to forgetting [15]. In addition, cued reactivation might accelerate the 'redistribution' of fresh memory traces from hippocampal to neocortical networks in a critical time window in order to achieve beneficial effects sooner, since re-exposure to odor cues in a 40 min sleep period increased memory performance to the same extent as a 90 min sleep period without external reactivation [16]. When auditory cues previously associated with pictures of faces were re-presented during rapid eye movement (REM) sleep, both accurate recollections and false recognitions were enhanced, suggesting that TMR also favors the generalization and schematization of information [20].

Declarative memory is the scaffold supporting other high order cognitive functions such as language learning, a process that has also been shown to be facilitated by sleep [21]. The potential applications of TMR were extended to include potentiation of foreign language learning, since verbal cueing during sleep improved later recall of foreign vocabulary [18]. These results were successfully replicated in a following study using the same experimental paradigm [19]. In addition, the latter study demonstrated that the beneficial effect of vocabulary cueing during sleep was abolished when immediate auditory feedback was provided after cueing, irrespective of the type of feedback. Notwithstanding, introducing a time delay between cue and auditory feedback preserved the memory enhancing effect of TMR. These results suggest that a certain time period is required after presentation of a cue to achieve stabilization and strengthening of a memory, since introducing a second auditory stimulus within this critical time window is likely to disrupt ongoing plasticity processes triggered by TMR [19].

Procedural memory

The vast majority of studies conducted so far using TMR have focused on hippocampus-dependent forms of memory, most likely because the success of this technique is thought to rely upon successive hippocampal reactivations. Since the hippocampus is also recruited during motor sequence learning [22], at least in theory, tasks probing a motor skill could prove to benefit from TMR. However, this is contradicted by the findings reported by Rasch and colleagues when an odor was used to target an explicitly learned motor sequence [13]. Regardless of the time of cueing, whether it took place during slow wave sleep (SWS), REM sleep or wakefulness, no significant improvements were found in comparison to an odorless vehicle. The authors argued that procedural skills such as the one probed with the finger tapping task might not be effectively conditioned to cues such as odors, which opened the question of whether or not the same applies to sounds [13].

To address this issue, a group of participants was submitted to musical training on two similar 12-item melodies, in a task similar to the video game *Guitar Hero* [23]. Notwithstanding, in this task, the sounds are an intrinsic component of the task itself, i.e., elicited in response to the motor behavior, and not just a sensory element present in the learning context [23]. The sensorimotor integration required for music learning is likely more heavily dependent on medial temporal lobe structures like the hippocampus [24,25] than a mere procedural task such as the finger tapping task, hence rendering it more suitable for an intervention like TMR. Indeed, cueing participants with one of the trained melodies during SWS periods in a daytime nap resulted in enhanced accuracy on the cued melody upon retrieval [23]. This result was confirmed in a subsequent study in which participants had to output a 12-item sequence paired with piano tones. During the following sleep episode, half of the sequence was replayed to the participants. At retest, an increase in accuracy was observed for the cued half of the sequence only [26]. These findings suggest that the neuronal replay induced by auditory cueing is highly