Title: How does Targeted Memory Reactivation selectively strengthen memories during sleep?

Penelope A. Lewis (1) and Daniel Bendor (2)

1) Psychology Department, Cardiff University
2) Department of Experimental Psychology, University College London

Over the last ten years, scientists have developed a method for selectively strengthening memories during sleep called targeted memory reactivation (TMR). Prior to this, memory manipulation during sleep was at most a plot device in science fiction movies, but a large corpus of studies now demonstrates that TMR is both reliable and effective. TMR studies hypothesize that this method taps into normal consolidation mechanisms which require the repeated replay of memories during sleep. This idea has recently been supported by several new studies demonstrating that TMR upregulates the reactivation of cued memories, and that such upregulation predicts subsequent memory performance. This new body of work provides a unique window onto many properties of memory reactivation and helps to close the gap between our understanding of replay in rodents, where it has been visualised at the neural level for many years, and humans where such studies are only just starting to become possible. We will discuss this new literature and highlight the vast potential of these new methods for future research.

Acknowledgements: DB is funded by an ERC Starting Grant: CHIME. PL is funded by an ERC Consolidator Grant: SolutionSleep. We are grateful to Lorena Santamaria Covariabus, Mahmoud Eid-Abdellahi and Lilia Kukovska for helpful input on the manuscript.

Our conscious minds rest while we sleep, but our brains remain active. Almost 50 years ago, David Marr postulated that recently acquired memories may reactivate during sleep for the purpose of consolidation [1]. While aspects of his model may have been oversimplified, Marr's theoretical framework for memory reactivation during sleep has been substantiated by the discovery of memory reactivation in both rodents [2,3] and humans [4–6], with stereotyped patterns of neural activity representing a recent behavioural episode spontaneously reactivating during sleep. In this review, we will discuss memory reactivation in sleep, and the burgeoning evidence that it can be actively biased by presenting sensory cues.

Memory reactivation in rodents

Preliminary evidence for the reactivation of memory traces during sleep came from observations in rodents that the firing rates of hippocampal neurons during behaviour tend to be correlated with firing rates of the same neurons during subsequent sleep [7]. The development of large-scale electrophysiological recordings soon made it feasible to observe neuronal ensembles firing in a stereotyped temporal sequence. Using this approach, reactivation was indexed via the correlation of spike timing between pairs of neurons. Thus, neurons that fired together during behaviour were more likely to fire together during non-REM sleep [2]. With more sophisticated analysis methods, observation of reactivating neuronal pairs was extended the reactivation of actual sequences within neuronal ensembles [3,8], **figure 1A** which is known as memory replay.

Memory replay has mainly been studied in the rodent hippocampus, where it occurs during sharp-wave ripple events, which are frequent in periods of rest and non-REM sleep. Such replay possesses several important properties including temporal compression: replays occur ~5-20x faster than actual events [3,8], context-specificity: hippocampal place cells remap their place fields between contexts, potentially helping prevent interference between replayed memories [9], coordination: hippocampal replay can be accompanied by cortical replay of the same event [10], and causality: manipulating sharp wave ripples such that replay is suppressed (or enhanced), results in impairment (or improvement) in memory consolidation [11,12]. Replay has also been observed during wake [13] and rapid eye movement (REM) sleep [14], however whether these forms of replay share the properties of hippocampal replay in non-REM sleep, and whether they are similar in function or at least complementary to non-REM sleep replay remain as open questions.

Memory reactivation in human sleep

Building on experiments in rodents, evidence of neural reactivation has also been identified in human sleep. Neuroimaging has shown that areas of the motor system associated with a finger tapping task spontaneously reactivate during REM [4], and that a hippocampal region

which activates during navigation around a virtual maze spontaneously reactivates during subsequent slow wave sleep (SWS) [5]. In the latter study, the extent of reactivation predicted the degree to which navigation improved across the night, providing the first evidence that reactivation may have a functional role in memory consolidation. In a more sensitive approach, electroencephalography (EEG) classifiers were used to detect reinstatement of neural patterns associated with viewing faces or houses during subsequent sleep [6], and the extent of such reinstatement predicted subsequent task performance. When integrating this human work with studies of rodent replay, it is important to point out that neuroimaging studies, which examine large populations of neurons, probe the system at a very different level of analysis from single-unit recordings in rodents. The apparent reinstatement observed in human studies could potentially be due to a completely different form of neural activity within the areas in question, such as processes associated with homeostatic downscaling rather than reactivation [15]. However, reinstatement has also been observed in humans at the single neural level in both cortex and hippocampus [16]. In addition, while the bulk of the human literature relates only to reactivation, sequential replay has also been observed in humans using Magnetoencephalography (MEG) during wake [17], though it has yet to be detected in sleep.

How can sensory stimulation in sleep influence reactivation?

Not all memory reactivation is spontaneous. Instead, a technique called Targeted Memory Reactivation, or TMR, is thought to manipulate reactivation on demand. In this method, sensory cues such as odours [18] or sounds [19] are paired with information during wake, and then re-presented during subsequent sleep. This can lead to a behavioural memory benefit, a result which seems to suggest that the manipulation may increase memory replay (see [18–21] for examples, [22] for a review, and **box 1**). One study [23] directly investigated this suggestion by training rats on a simplified TMR-style task where auditory cues were used to initiate leftward or rightward trajectories. During non-REM sleep, presentation of an auditory cue resulted in increased replay of the cued trajectory. However, presentation of the cue did not evoke replay events or increase the total number of such events. This suggests that task-related cues only increase the likelihood that the cued trajectory would replay, an effect that lasted at least ten seconds after each sound, or until another sound was played. These findings support the idea that TMR influences what is replayed, but doesn't increase the total number of replays. This is also supported by TMR studies in humans since performance on non-cued items is worse than it would be if no TMR had been applied, suggesting that TMR cued benefit to one memory comes at the cost of non-cued memories [20,21].

As sleep architecture and hippocampal properties differ markedly between humans and rodents [24] it isn't immediately clear that TMR in humans necessarily influences replay in the

same way as it does in rodents. One tantalising study [25] showed that TMR cues associated with objects and scenes respectively lead to highly discriminable patterns in the post-cue EEG (see **Figure 1B** top). Interestingly, the extent of this discriminability also predicted subsequent behavioural benefit from TMR. However, the discriminability in sleep was not based on any measure in wake, so these data cannot be taken as a measure of reactivation. The first study to demonstrate actual reactivation of task-specific responses after a TMR cue in sleep [26] used a serial reaction time task, in which participants learned to associate each of four fingers with a different tone and picture, and to press the associated buttons in a sequence cued by these tone/picture stimuli. In the experimental condition, a classifier was trained to discriminate the EEG associated with each finger press while participants experienced these sensory cues. The tones were then replayed during subsequent sleep, and the wake-trained classifier was applied to the sleep data following each tone. Remarkably, this led to above chance classification of which finger movement was cued by each tone, even though the participant was asleep. Because such classification could potentially be due to sensory processing of the tones themselves, the study used a control group in which tones were played during wake exactly as in the experimental condition, but with no task or image associated. The classifier was trained on these control tones using the exact same pipeline that had been applied in the experimental condition, but was unable to distinguish between the tones. Given this control, successful discrimination by the experimental classifier during sleep is most likely due to detection of reactivating task-related material (e.g. memories of the visual images and finger movements) elicited by the tones, not to sensory processing of the tones themselves. Following this work, Schreiner et al [27] used a phase locking measurement in the theta frequency band to demonstrate that neural activity patterns associated with learned vocabulary word pairs were reinstated when the cue words were played back during NREM sleep. Reactivation was only detected for the pairs that were subsequently remembered – not those subsequently forgotten. Interestingly, the reactivation occurred up to three times after the TMR cue, echoing back roughly once per second. However, there was no control condition in this study, so the reactivation-like pattern observed here could potentially be due to sensory processing, making the results difficult to interpret. In addition to these EEG studies, a recent fMRI study [28] showed that the extent to which ventromedial prefrontal cortex voxels reactivated in response to odour TMR predicted the extent of overnight increases in recall accuracy. Here, reactivation was indexed by the similarity of the post-odour response pattern to a pattern elicited during wakeful experience of the category associated with that odour (see **figure 1, box 1**).

This growing literature on the detection of reactivation in humans provides invaluable information about the activity elicited by TMR cues (see **box 1**). This literature also provides

a brand new set of tools for studying reactivation in the human cortex. In EEG and MEG data, these include Linear Discriminant Classifiers applied to signal amplitude [29], as well as to wavelet and Fourier transformed data [26], lasso logistic regression [17], Representation Similarity Analysis [25,30]), Independent Component Analysis (ICA) based feature selection [25], microstates analysis, and Phase Locking Values [27] . In fMRI data, Multi Voxel Pattern Similarity Analyses (MVPA) has proved very useful [28]. Together, these tools should facilitate the optimisation of TMR by working out which types of cues most effectively influence reactivation, the study of TMR in different sleep stages to determine whether the associated reactivations have different characteristics, and the search for a mapping between the number and strength of reactivations and subsequent plasticity – both behavioural and functional. We should also be able to use variants of these techniques to search for temporal compression in cortical reactivation during sleep.

As we begin to apply these new methods to the study of reactivation in the human brain, it may be interesting to bear in mind the four hallmark features of hippocampal replay in rodents: *compression, coordination, context-specificity,* and *causality,* in order to determine whether these are shared by human reactivation.

Why does TMR bias replay?

TMR appears to protect or strengthen memories by biasing the hippocampus to replay them during sleep, but how does this work? In the standard model of consolidation [31], the hippocampus stores cortical information during behaviour, then during off-line periods such as sleep these memories are replayed back to neocortex for long term storage. Information is hypothesized to flow uni-directionally from hippocampus to cortex during sharp-wave ripple events, within which replay is observed [32]. However accumulating evidence suggests that cortical-hippocampal interactions may be more complicated, given that increases in cortical activity often occur prior to hippocampal replay [10,33,34]. Interestingly, cortical activity prior to hippocampal reactivation has also been shown to predict the content of subsequent hippocampal reactivation [35]. As sensory cues still evoke neocortical activity during sleep [36], TMR may effectively trick the hippocampus by evoking what looks like a spontaneous reactivation of a memory in cortex and in turn influence what the hippocampus replays.

Why would memory consolidation rely on cortical inputs to the hippocampus? A recent model [37] proposed by Rothschild suggests that cortical input is part of a cortico-hippocampal-cortical loop, which strengthens a memory through the reverberation of replay between the cortex and hippocampus. Because the hippocampus encodes spatiotemporal context, while other aspects of the memory such as emotional valence and sensory components are encoded in cortex, the reverberation of a replay event helps bind these different components

together to form a coherent memory. According to this model, a cortical memory representation reactivates during the 'up' state of a slow oscillation, and triggers a hippocampal replay of the same memory, allowing integration of this information across space and time. This integrated representation is then sent back to the cortex for a second reactivation, with the repetition of this pattern potentially creating a series of temporally spaced hippocampal-cortical reactivations. Interestingly, this model is in line with the pattern of 'echoing' reactivations observed by Schreiner et al [27] and others [25,38] in cortical-dominated EEG data, see **Figure 1B**. These results probably reflect both an initial cortical response immediately after the TMR cue, and secondary and even tertiary responses. Under the Rothschild model, these latter 'echoes' could potentially represent genuine replays triggered in the cortex by the hippocampus.

Building on this model, we propose that this cortico-hippocampal-cortical loop could serve as a mechanism for memory triage, a sleep-dependent process by which memories with perceived future relevance are prioritized for consolidation [39,40], see **Figure 2**. We propose that, during behaviour, cortical networks associated with a memory may be tagged in a way that indicates their salience, and thus their priority for subsequent consolidation [34,41]. Such tagging could manifest as increased excitability during a non-REM up state, and this excitability could scale based on the behavioural relevance of the tagged information. Thus, the excitation of salient cortical networks in an up state could contribute to the task-related cortical activity observed prior to spontaneous hippocampal replay [10,35,42]. Such cortical excitation could potentially represent multiple cortical networks "competing" to determine which memory will be replayed by the hippocampus. We speculate that repeated replay events (or post-replay activity) could gradually decrease the strength of the 'tag' associated with a cortical network, thus decreasing that network's excitability. This would create a prioritization trade-off between how many times a memory has been replayed and its salience relative to other recent memories, and would thus form a critical feedback mechanism for the memory triage process.

Closing Remarks

This is an exciting era for neuroscience, and the story of how memories evolve via replay and reinstatement is one of the most striking areas of progress. Many questions remain to be answered, but the development of TMR, in combination with the new methods for detection of neural reactivation on a trial by trial basis in humans has provided us with a promising way forward. In many ways, the study of memory reactivation in the human brain is following directly in the footsteps of earlier studies in rodents. For example, a recent report of awake replay in humans, provides evidence of several key hallmarks of rodent replay including

sequential reactivation, temporal compression, replay alignment with hippocampal ripple activity, and coordination between the hippocampus and neocortex [17]. However, we have yet to detect true sequential replay during sleep, though this seems the inevitable next step. Similarly, we have yet to understand interactions between the hippocampus and neocortex during replay, and to detect replay during REM sleep in humans. As with so many areas of science, it is clear that human and animal researchers will need to work closely, and in this case such collaboration seems to be leading to a renaissance of studying the replay phenomena, now focused on the human brain.

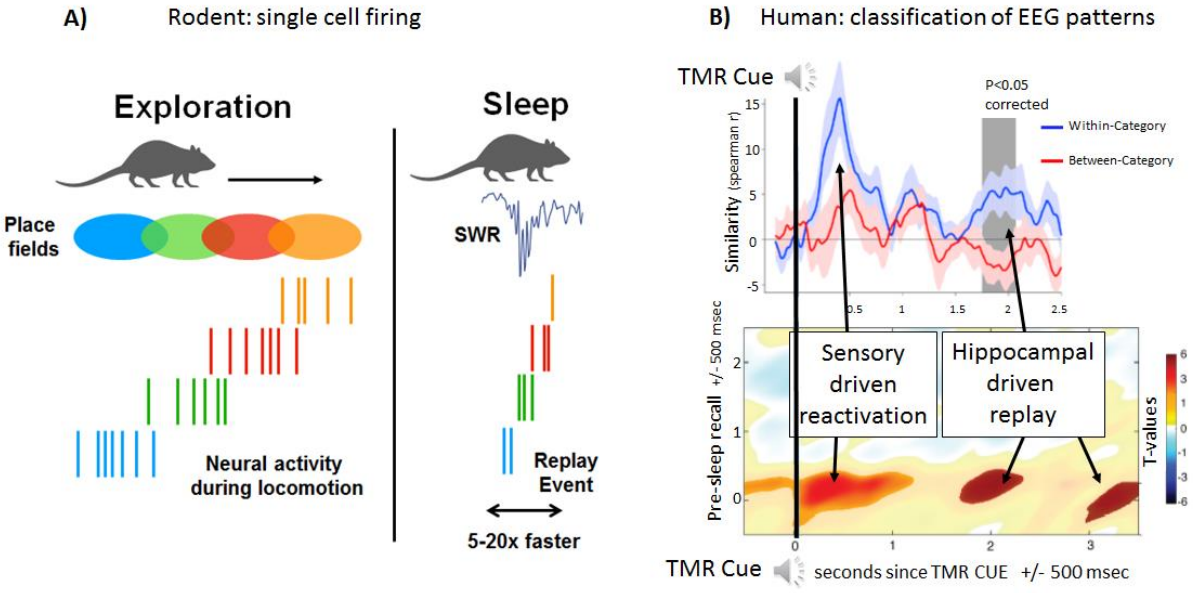


Figure 1. Neural reinstatement in sleep. **A)** Schematic of place cell firing during locomotion on a linear track and then, in a temporally compressed form, during subsequent sleep, concurrent with a sharp-wave ripple (SWR). **B)** Identification of cue-related reinstatement in sleep in EEG data shows a recurrent pattern. **Top**: Cairney et. al. 2018 [25] shows the discriminability of EEG data following auditory TMR of memories for objects or scenes. Discriminability is higher between than within categories at both ~0.5 seconds and 2 seconds post cue. **Bottom**: Schreiner et. al. 2018 [27] use Phase Locking values to detect reinstatement of patterns form wakeful retrieval in response to word cues. Evidence for reinstatement occurs immediately after the TMR cue, then echoes back two more times, spaced approximately a second apart. We speculate that reactivation directly after TMR may be due to the potentiation of cortical areas which represent part of a memory trace, while the subsequent 'echoes' may represent more complete replays triggered by hippocampal ripples.

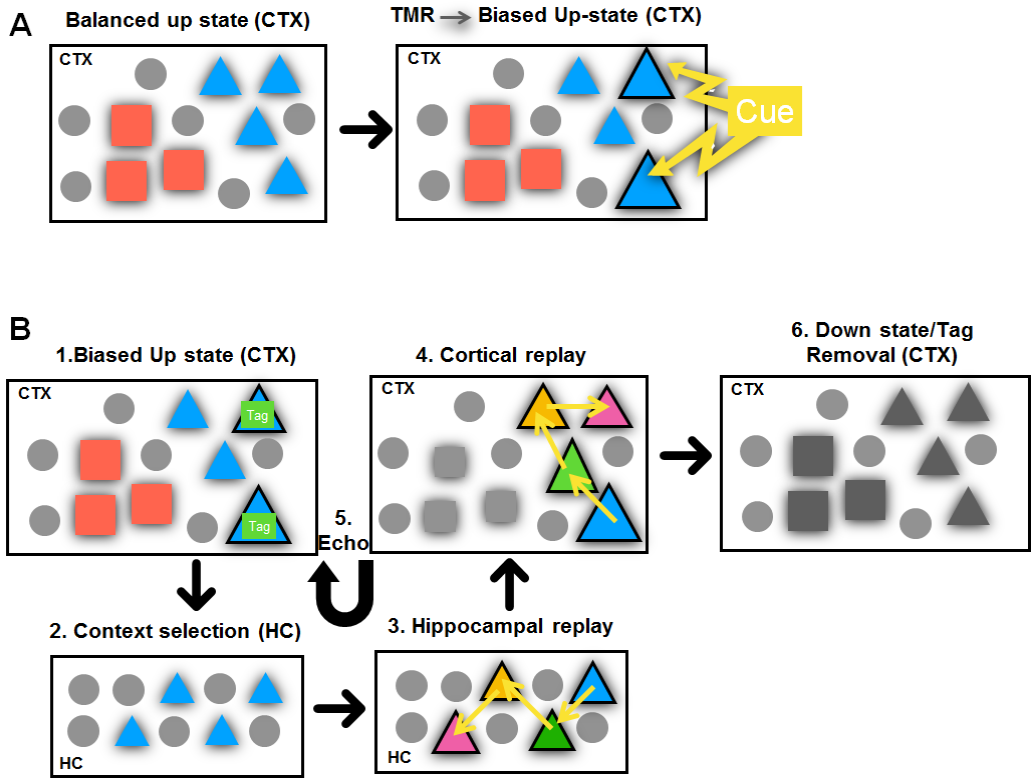


Figure 2. Proposed mechanism for cortical biasing of hippocampal replay in non-REM sleep. **A)** TMR: Presentation of a cue during TMR increases the activity of cortical neurons associated with the cued-memory during an upstate, this subsequently biases hippocampal replay as shown in B. **B)** The role of cortical feedback in memory triage: **1.** Strongly tagged cortical networks (or neurons activated by TMR) increase their activity during a cortical upstate. **2**. The cortical network with the greatest activity determines which context will be represented by the hippocampus. **3.** Hippocampal replay occurs spontaneously, reactivating a sequence related to the selected context. **4.** Hippocampal replay drives cortical replay of the same memory, complete with sequential information. **5.** Additional hippocampal-cortical replay can occur (echoes) while cortical neurons remain in an up state. **6.** Following replay, the tag in cortical neurons which were recently involved in a replay is weakened, reducing the priority for them to replay again, and this cycle is repeated in the next cortical up-state.

BOX 1 - Targeted Memory Reactivation – what has been learned from classifiers

Memories are replayed spontaneously in sleep, but is it possible to control this process by biasing the replay towards specific memories? A landmark study by Rasch and colleagues [18] demonstrated that it is. In this study, re-presentation of an odour that had been previously associated with learned locations during subsequent NREM sleep led to hippocampal activity in sleep and subsequent memory benefit. This method of re-presenting a memory associated cue during sleep was assumed to bias memory reactivation, and was dubbed Targeted Memory Reactivation or TMR. Subsequent studies showed that auditory cues could be used in place of odour [19], and that procedural as well as episodic memories could be enhanced [20]. Other work showed that TMR effects can last for over a week [19], and involve qualitative as well as quantitative changes in memory [21]. Importantly, TMR does not always lead to significant results. Nevertheless, it has substantial potential for translation, both in healthy and clinical populations where selective memory improvement would be beneficial. While other authors comprehensively review this literature, e.g. [22], our focus is on the recent work which has used machine learning to detect reactivation after TMR cues. Some of the key features identified by these methods are outlined below. As this is a very new area, it will be interesting to see if these properties are supported in the future.

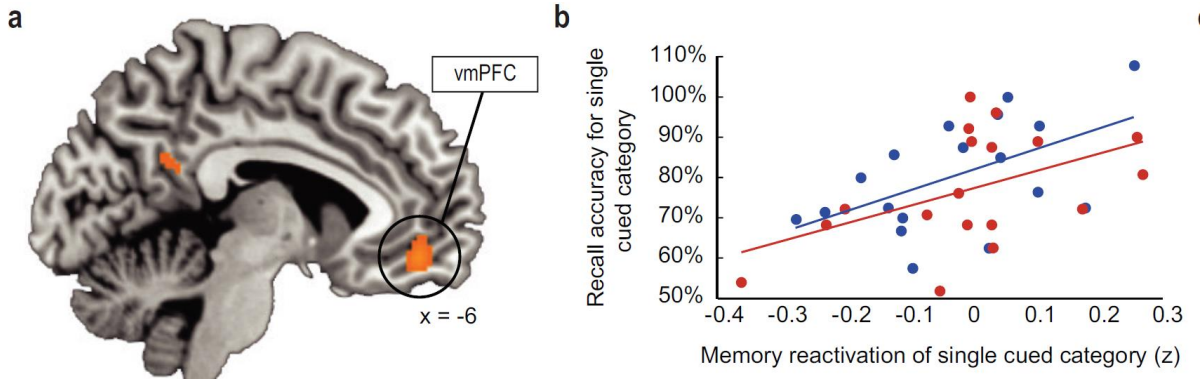
Key features of TMR cued Reactivation:

Reactivation after TMR is identifiable: recent work shows that TMR is often followed by cortical reactivation of memories associated with the cued experience [26–28,38].

Reactivation in sleep predicts subsequent memory: the extent to which reactivation is measurable after TMR predicts subsequent memory [28,38,43], see **Figure 1,** and/or is stronger for subsequently remembered than forgotten items [27,38]. This is also true for spontaneous reactivation [6,30], although some studies have also found a negative relationship [44].

Echoing of reactivation after TMR: cortical reactivation recurs several times after TMR [27,38,43]. In rats, the TMR induced bias in hippocampal replay continues until another cue is played [23]. It is possible that the first cortical response is represents a partial trace, while subsequent ‘reactivations’ are triggered by the hippocampus and more complete.

Relationship of reactivation to spindles: reactivation may occur during sleep spindles [25, 43], see **Box 2**, and TMR cues are less likely to elicit reactivation if they occur too soon after a spindle [38].



Box 1, Figure 1. From Shanahan et. al. 2019 [28], this figure shows (**A**) a region of ventromedial prefrontal cortex (vmPFC) which strongly reactivates category information (faces, buildings, animals, tools) in response to odour TMR during slow wave sleep. **B**) Significant correlation between the extent of vmPFC reactivation and subsequent recall accuracy for that category. The blue and red dots represent two different categories, each showing the same correlation.

BOX 2: How do sleep spindles relate to memory replay?

Sleep spindles are tightly linked to memory consolidation. This has been shown by many correlational studies, see [45] for a review, as well as several manipulations in which spindle enhancement lead to greater memory consolidation [46,47]. Indeed, there is a tight correlation between the hippocampal sharp-wave ripples during which memory replay occurs, and sleep spindles [34]. This link has been supported by the new human literature on identifying reactivation with classifiers. Specifically, strong evidence for category related activity after TMR of a picture recognition task has been detected during spindles two seconds after TMR [25]. Additionally, evidence for reactivation of a right or left handed finger press was observed to increase with post-cue spindle power and cues followed by spindles were better remembered than cues without a spindle [38]. Related to this, a brain area which was active during pre-sleep encoding and post sleep retrieval was also active during fast spindles in sleep, with the extent of such activity predicting overnight performance change [48]. This latter result builds on a prior study showing that the extent of pre-sleep learning modulates the interaction between fast spindles and hippocampus during Non-REM sleep [49]. In keeping with this literature, a prominent model [45] proposes that replay is concurrent with spindles. Human intracranial data from hippocampal recordings has supported this by describing ripples nested in the troughs of spindles [29]. Nevertheless, the rodent literature suggests that the relationship between ripples and spindles is complex, and we should be careful about generalising. For instance, this work reveals that hippocampal sharp-wave ripples often precede prefrontal cortical spindles by more than a second [34]. Interestingly, spindles are associated with inhibition [43,50] and it has been suggested that they play a role in preventing interference, thus allowing plasticity resulting from recent replays to occur without disruption. In summary, while spindles are almost certainly related to replay, it would be an oversimplification to think of them as concurrent ‘markers’ of replay, and much remains to be understood about their role in memory consolidation.

REFERENCES

1. Marr, D. (1971). Simple memory: a theory for archicortex. Philos.Trans. R. Soc. L. B Biol. Sci. *262*, 23–81.
2. Wilson, M.A., and McNaughton, B.L. (1994). Reactivation of hippocampal ensemble memories during sleep. Science (80). *265*, 676–679.
3. Lee, A.K., and Wilson, M.A. (2002). Memory of sequential experience in the hippocampus during slow wave sleep. Neuron *36*, 1183–1194.
4. Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., Aerts, J., Del, F.G., Degueldre, C., Meulemans, T., *et al.* (2000). Experience-dependent changes in cerebral activation during human REM sleep. Nat.Neurosci. *3*, 831–836.
5. Peigneux, P., Laureys, S., Fuchs, S., Collette, F., Perrin, F., Reggers, J., Phillips, C., Degueldre, C., Del Fiore, G., Aerts, J., *et al.* (2004). Are spatial memories strengthened in the human hippocampus during slow wave sleep? Neuron *44*, 535–545.
6. Schönauer, M., Alizadeh, S., Jamalabadi, H., Abraham, A., Pawlizki, A., and Gais, S. (2017). Decoding material-specific memory reprocessing during sleep in humans. Nat. Commun. *8*, 15404. Available at: http://www.nature.com/doifinder/10.1038/ncomms15404.
7. Pavlides, C.., and Winson, J. (1989). Influences of hippocampal place cell firing in the awake state on the activity of these cells druing subsequent sleep episodese. J. Neurosci. *9*, 2907–2918.
8. Foster, D.J. (2017). Replay Comes of Age. Annu. Rev. Neurosci. *40*, 581–602. Available at: http://www.annualreviews.org/doi/10.1146/annurev-neuro-072116-031538.
9. Leutgeb, S., Leutgeb, J.K., Barnes, C.A., Moser, E.I., McNaughton, B.L., and Moser, M.B. (2005). Neuroscience: Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. Science (80). *309*, 619–623.
10. Ji, D., and Wilson, M.A. (2007). Coordinated memory replay in the visual cortex and

hippocampus during sleep. Nat. Neurosci. *10*, 100–107.

11. Fernández-Ruiz, A., Oliva, A., Fermino de Oliveira, E., Rocha-Almeida, F., Tingley, D., and Buzsáki, G. (2019). Long-duration hippocampal sharp wave ripples improve memory. Science (80). *364*, 1082–1086. Available at: http://www.sciencemag.org/lookup/doi/10.1126/science.aax0758.
12. Girardeau, G., Benchenane, K., Wiener, S.I., Buzsaki, G., Zugaro, M.B., and Buzsáki, G. (2009). Selective suppression of hippocampal ripples impairs spatial memory. Nat.Neurosci. *12*, 1222–1223.
13. Foster, D.J., and Wilson, M.A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature *440*, 680–683.
14. Louie, K., and Wilson, M.A. (2001). Temporally Structured Replay of Awake Hippocampal Ensemble Activity during Rapid Eye Movement Sleep. Neuron *29*, 145–156. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0896627301001866.
15. Huber, R., Ghilardi, M.F., Massimini, M., and Tononi, G. (2004). Local sleep and learning. Nature *430*, 78–81.
16. Gelbard-sagiv, H., Mukamel, R., Harel, M., Malach, R., and Fried, I. (2008). Internally generated reactivation of single neurones in human hippocampus during free recall. Science (80). *322*, 96–101.
17. Liu, Y., Dolan, R.J., Kurth-nelson, Z., and Behrens, T.E.J. (2019). Article Human Replay Spontaneously Reorganizes Experience. 1–13.
18. Rasch, B., Buchel, C., Gais, S., and Born, J. (2007). Odor Cues During Slow-Wave. Science (80)., 1426–1429.
19. Rudoy, J.D., Voss, J.L., Westerberg, C.E., and Paller, K.A. (2009). Strengthening individual memories by reactivating them during sleep. Science (80). *326*, 1079.
20. Antony, J.W., Gobel, E.W., O'Hare, J.K., Reber, P.J., and Paller, K.A. (2012). Cued memory reactivation during sleep influences skill learning. Nat.Neurosci. *15*, 1114–6.
21. Cousins, J.N., El.Deredy, W., Parkes, L.M., Hennies, N., and Lewis, P.A. (2014). Cued memory reactivation during slow-wave sleep promotes explicit knowledge of a

motor sequence. J. Neurosci. *34*, 15870–15876. Available at: http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.1011-14.2014 [Accessed November 27, 2014].

22. Cellini, N., and Cappuzo, A. (2018). Shaping memory consolidation via targeted memory. Ann. N. Y. Acad. Sci. *1426*, 52–71.
23. Bendor, D., and Wilson, M.A. (2012). Biasing the content of hippocampal replay during sleep. Nat. Neurosci. *15*, 1439–44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22941111%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4354843.
24. Mölle, M., Eschenko, O., Gais, S., Sara, S.J., and Born, J. (2009). The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. Eur. J. Neurosci. *29*, 1071–1081.
25. Cairney, S.A., Guttesen, A. á. V.V., El Marj, N., and Staresina, B.P. (2018). Memory Consolidation Is Linked to Spindle-Mediated Information Processing during Sleep. Curr. Biol. *28*, 948-954.e4. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0960982218301532.
26. Belal, S., Cousins, J., El-deredy, W., Parkes, L., Schneider, J., Tsujimura, H., Zoumpoulaki, A., Perapoch, M., Santamaria, L., and Lewis, P. (2018). Identification of memory reactivation during sleep by EEG classification. Neuroimage *176*, 203–214.
27. Schreiner, T., Doeller, C.F., Jensen, O., Rasch, B., and Staudigl, T. (2018). Theta Phase-Coordinated Memory Reactivation Reoccurs in a Slow-Oscillatory Rhythm during NREM Sleep. Cell Rep. *25*, 296–301.
28. Shanahan, L.K., Gjorgieva, E., Paller, K.A., Kahnt, T., and Gottfried, J.A. (2018). Odor-evoked category reactivation in human ventromedial prefrontal cortex during sleep promotes memory consolidation. Elife, 1–21. Available at: https://elifesciences.org/articles/39681.
29. Staresina, B.P., Ole Bergmann, T., Bonnefond, M., van der Meij, R., Jensen, O., Deuker, L., Elger, C.E., Axmacher, N., and Fell, J. (2015). Hierarchical nesting of slow

oscillations, spindles and ripples in the human hippocampus during sleep. Nat. Neurosci. *18*, 1679–1686.

30. Zhang, H., Fell, J., and Axmacher, N. (2018). Electrophysiological mechanisms of human memory consolidation. Nat. Commun. *9*. Available at: http://dx.doi.org/10.1038/s41467-018-06553-y.

31. Squire, L.R., and Alvarez, P. (2001). Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr. Opin. Neurobiol. *5*, 169–177.

32. Buzsaki, G. (1989). Two-stage model of memory trace formation: a role for "noisy" brain states. Neuroscience *31*, 551–570.

33. Sirota, A., Csicsvari, J., and Buhl, D. (2003). Communication between neocortex and hippocampus. Proc. Natl. Acad. Sci. U. S. A. *100*, 2065–2069. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12576550.

34. Peyrache, A., Khamassi, M., Benchenane, K., Wiener, S.I., and Battaglia, F.P. (2009). Replay of rule-learning related neural patterns in the prefrontal cortex during sleep. Nat.Neurosci. *12*, 919–926.

35. Rothschild, G., Eban, E., and Frank, L.M. (2017). A cortical – hippocampal – cortical loop of information processing during memory consolidation. Nat. Neurosci. *20*, 251–259.

36. Issa, E.B., and Wang, X. (2008). Sensory Responses during Sleep in Primate Primary and Secondary Auditory Cortex. J. Neurosci. *28*, 14467–14480.

37. Rothschild, G. (2019). The transformation of multi-sensory experiences into memories during sleep. Neurobiol. Learn. Mem. *160*, 58–66.

38. Wang, B., Antony, J.W., Lurie, S., Brooks, P.P., Paller, K.A., and Norman, K.A. (2018). Targeted memory reactivation during sleep elicits neural signals related to learning content. bioRxiv, http://dx.doi.org/10.1101/449389doi.

39. Stickgold, R., and Walker, M.P. (2013). Sleep-dependent memory triage: Evolving generalization through selective processing. Nat. Neurosci. *16*, 139–145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23354387 [Accessed September 23, 2014].

40. Rauchs, G., Feyers, D., Landeau, B., Bastin, C., Luxen, A., Maquet, P., and Collette, F. (2011). Sleep Contributes to the Strengthening of Some Memories Over Others, Depending on Hippocampal Activity at Learning. J. Neurosci. *31*, 2563–2568.

41. Lesburgueres, E., Gobbo, O.L., Alaux-cantin, S., Hambucken, A., Trifilieff, P., and Bontempi, B. (2019). Early Tagging of Cortical Networks Is Required for the Formation of Enduring Associative Memory. *331*, 924–928.

42. Isomura, Y., Sirota, A., Özen, S., Montgomery, S., Mizuseki, K., Henze, D.A., and Buzsáki, G. (2006). Integration and Segregation of Activity in Entorhinal-Hippocampal Subregions by Neocortical Slow Oscillations. Neuron *52*, 871–882.

43. Antony, J.W., Schönauer, M., Staresina, B.P., and Cairney, S.A. (2018). Sleep Spindles and Memory Reprocessing. Trends Neurosci. *42*, 1–3. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0166223618302583.

44. Murphy, M., Stickgold, R., Parr, M.E., Callahan, C., and Wamsley, E.J. (2018). Recurrence of task-related electroencephalographic activity during post-training quiet rest and sleep. Sci. Rep. *8*, 1–10. Available at: http://dx.doi.org/10.1038/s41598-018-23590-1.

45. Rasch, B., and Born, J. (2013). About sleep's role in memory. Physiol Rev *93*, 681–766.

46. Lustenberger, C., Michael, R., Alagapan, S., Mellin, J.M., Vaughn, B. V, Lustenberger, C., Boyle, M.R., Alagapan, S., Mellin, J.M., and Vaughn, B. V (2016). Feedback-Controlled Transcranial Alternating Current Stimulation Reveals a Functional Role of Sleep Spindles in Motor Memory Consolidation. Curr. Biol. *26*, 2127–2136.

47. Ngo, H.V., Martinetz, T., Born, J., Molle, M., and Mölle, M. (2013). Auditory closed-loop stimulation of the sleep slow oscillation enhances memory. Neuron *78*, 545–553.

48. Jegou, A., Schabus, M., Gosseries, O., Dahmen, B., Desseilles, M., Sterpenich, V., Phillips, C., Maquet, P., Grova, C., and Dang-vu, T.T. (2019). Cortical reactivations during sleep spindles following declarative learning. Neuroimage *195*, 104–112.

49. Bergmann, T.O., Mölle, M., Diedrichs, J., Born, J., and Siebner, H.R. (2012). Sleep

spindle-related reactivation of category-specific cortical regions after learning face-scene associations. Neuroimage *59*, 2733–2742. Available at: http://dx.doi.org/10.1016/j.neuroimage.2011.10.036.

50. Peyrache, A., Dehghani, N., Eskandar, E.N., Madsen, J.R., and Anderson, W.S. (2012). Spatiotemporal dynamics of neocortical excitation and inhibition during human sleep. *109*.