ISSN: 3066-716X
Short Review
Journal of Clinical and Biomedical Advances

Memory Replay, Reinforcement Learning and Therapeutic Implications

Panagiota Stritsou

2nd Neurological Department, University General Hospital of Thessaloniki "AHEPA", Thessaloniki, Greece

***Corresponding author:** Panagiota Stritsou, 2nd Neurological Department, University General Hospital of Thessaloniki "AHEPA", Thessaloniki, Greece.

Submitted: 15 June 2025 **Accepted:** 22 June 2025 **Published:** 27 June 2025

https://doi.org/10.63620/MKJCBA.2025.1044

Citation: *Stritsou, P. (2025). Memory Replay, Reinforcement Learning and Therapeutic Implications. J of Clin Bio Med Adv, 4(3), 01-03.*

Abstract
Memory replay is a process mainly taking place in the hippocampus where it is mediated by Sharp Wave Ripples (SWRs). Memory replay leads to memory consolidation, and it can be seen in both sleep and awake states and furthermore it can unfold in the forward or reverse direction. The reverse memory replay is thought to underly the process of reinforcement learning. Further investigations are needed regarding the exact underlying mechanisms of SWRs and memory replay, because they could be targets for innovative therapeutic interventions.

Keywords: Memory Replay, Hippocampus, Sharp Wave Ripples, Reinforcement Learning.

Introduction

The human brain shows modularity, with separate subsystems, that interact. Memory is based on different structures and processes. One aspect of human memory is episodic memory, along with reinforcement learning, which are functions mediated by the hippocampus. Although there is a recent breakthrough, by using structural and functional brain imaging, there are only theories and models of memory and many questions about how actually, memory function, is accomplished.

The term episodic memory is referring to memories, of previous life experiences. In order episodic memory to be fulfilled, processes like perception of information, encoding of information, storage of information and retrieval of appropriate information, need to be realized. These processes are mediated by circuits in the medial temporal lobe that allow experiences to be encoded rapidly, in a content - addressable store [1-3]. On the other hand, reinforcement learning refers to learned behaviors, based on previous experiences which resulted in rewards or punishments.

Memory Replay and Sharp Wave Ripples

Hippocampus is a hub of large cortical circuits (ventral and dorsal streams), in which information from previous stages is integrated in the next stages, through back projections [4]. Post-encoding processes during sleep lead to consolidation of memories, acquired during the previous day [4]. Memory consolidation is the transformation of an unstable memory to a long-lasting stable memory [5]. In the process of consolidation, a replay of information takes place in hippocampus and neocortex [5]. Wilson and McNaughton(1994), recorded spatial firing of hippocampal pyramidal cell populations in rats, during spatial behavioral tasks and during sleep, and showed that information gained during the activity period, was recapitulated during the sleep period [6]. This phenomenon, which is known as memory replay, today is thought to serve reactivation of past memories and underly hippocampal-cortical dialogue [7]. Place cells in the hippocampus encode information regarding places, directions and speed of movement, and their role in spatial navigation has been established both in rats and humans [8].

Sharp-wave ripples (SWRs) are bursts of neuron populations in the CA1, the CA3, the dentate gyrus and the subiculum of the hippocampus that occur during disinhibition of extrahippocampal inputs [9, 10]. SWRs are generated in CA3 with the involvement of NMDA glutamate receptors and changes in CA3 network, then they propagate to CA1 and subiculum [11]. They also require AMPA and Kainate type, glutamate receptors [11]. Low- frequency stimulation can block SWRs generation, but NMDA receptor antagonists can't block their generation [11].

In rats SWRs have been found in slow wave sleep, awake immobility, drinking, grooming and eating [4]. In humans SWRs, have been described in the entorhinal cortex and in the hippocampus (80-160 Hz) [12]. SWRs are thought to underly the transfer of memory traces from the hippocampus to the entorhinal cortex [13].

Memory Replay and it's Utility in Sleep and Awake States

Memory replay is a process that can be seen offline during sleep or quiet rest, but it could also be seen online during awake states [14]. Memory replay in awake states underlies processes like learning and memory-guided decision making [15]. Consolidation of memory can take place in both awake and sleep states [5].

Hippocampal replay unfolds in the forward direction, but also it can involve the backward direction [16]. Sequences of place cells firing, are replayed during sharp-wave hippocampal activity in the forward or in the reverse order [17, 18] Why is it necessary memory replay to be realized in two directions? It is believed that forward replay serves memory consolidation and planning, while backward replay serves reinforcement learning [19, 20]

Reinforcement Learning

According to a theory, learning is based in parallel or "complementary" learning systems in the hippocampus and neocortex [2, 21, 22]. The brain uses past experience, to make good decisions, in order to maximize future rewards [23]. One of the difficulties that might arise in reinforcement learning, is how to select the relevant states and actions, between the large amount of noise and sensory information, coming from the environment. One possible solution to this problem is that an attribute of a stimulus, like color, shape or motion is selected, because it is associated with a reward and that attribute can be used in reinforcement learning [23]. A version of the environment, based on some attributes, simplifies the large state-space encoding problem and the representation of a state by its similarity to other states, could solve the problem [23].

Therapeutic Implications

SWRs are responsible for transporting information from short term memory in the hippocampus to neocortex, where long term memory is stored. Girardeau et al. (2009) studied rats with a spatial memory task and found low performance, when SWRs were selectively eliminated, and this finding shows that SWRs are important for memory consolidation [24]. If selective suppression of SWRs leads to impaired long-term memory formation, then the question that arises is what happens in the case of enhancement of SWRs. Behrens et al. (2005) showed that by applying stimuli that induce long term potentiation (LTP) in rat hippocampal slices, SWRs were generated, with similar properties to spontaneous generated SWRs. These findings imply, that if LTP is applied in the hippocampal CA3 network the generation of SWRs may be facilitated [11].

Cholinergic impairment characterizes Alzheimer disease. Zhang et al. (2021) applied optogenetic manipulation in Acetylcholine (Ach) neurotransmitter, and found that the brain state during the time of the intervention defines the result, and that memory is supported not only by theta oscillations but also by SWRs [25].

A study by Nour et al. (2021) showed reduced memory replay and enhanced ripple power, regarding inferred relationships for object structures, in schizophrenic patients compared to healthy controls [26].

Reward reinforcement learning is connected to the dopaminergic system in the ventral tegmental area (VTA) of the midbrain. The reward prediction error by dopamine neurons, lead to different behaviors according to the relevant stimulus, with the ultimate goal of better adaptation, for humans and animals, in the physical and social environment [27, 28]. Miyawaki et al. (2014), showed that dopamine receptor activation led to an increase of frequency and magnitude in hippocampal SWRs and this finding indicates that dopaminergic activation reorganizes neuronal ensembles during SWRs [29].

Further elaboration of these findings can lead to considerations about possible therapeutic applications. The manipulation of suppression or enhancement of SWRs could lead to therapies for dementia, psychiatric disorders and Parkinson disease. It is possible that the reverse replay manipulation could be used in Parkinson disease, but right now it is not clear whether possible manipulations could impact only the memory deficits of these patients, or they could have an impact on the actual movement disorder.

How can this manipulation be realized? Possibly by common drug forms or drugs in the form of nanoparticles, that can act on the receptors or neurotransmitters, that are responsible for SWRs and memory replay. Optogenetics is a powerful tool that has been used to manipulate memory replay [30]. Other interventions could involve the application of electrical brain stimulation.

Conclusion

The above studies suggest that impairments in memory replay are involved in psychiatric disorders and dementias and possibly movement disorders. Further studies are needed to clarify the underlying mechanisms. Right now, there is much theoretical and experimental work that has to be done. Relevant knowledge could lead to innovative therapeutic interventions.

Conflict of Interest

None.

References

1. Gallistel, C. R., & King, A. P. (2009). Memory and the computational brain: Why cognitive science will transform neuroscience. Wiley-Blackwell.
2. Hassabis, D., Kumaran, D., Summerfield, C., & Botvinick, M. (2017). Neuroscience-inspired artificial intelligence. Neuron, 95(2), 245-258. https://doi.org/10.1016/j.neuron.2017.06.011
3. Squire, L. R. (2004). Memory systems of the brain: A brief history and current perspective. Neurobiology of Learning

and Memory, 82(3), 171-177. https://doi.org/10.1016/j.nlm.2004.06.005
4. Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic memory and beyond: The hippocampus and neocortex in transformation. Annual Review of Psychology, 67, 105-134. https://doi.org/10.1146/annurev-psych-113011-143733
5. Squire, L. R., Genzel, L., Wixted, J. T., & Morris, R. G. (2015). Memory consolidation. Cold Spring Harbor Perspectives in Biology, 7(8), a021766. https://doi.org/10.1101/cshperspect.a021766
6. Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. Science, 265, 676-679.
7. Huang, Q., Xiao, Z., Yu, Q., Luo, Y., Xu, J., Qu, Y., …& Liu, Y. (2024). Replay-triggered brain-wide activation in humans. Nature Communications, 15(1), 7185. https://doi.org/10.1038/s41467-024-51582-5
8. O'Keefe, J., Burgess, N., Donnett, J. G., Jeffery, K. J., & Maguire, E. A. (1998). Place cells, navigational accuracy, and the human hippocampus. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 353, 1333-1340.
9. Buzsáki, G. (1986). Hippocampal sharp waves: Their origin and significance. Brain Research, 398, 242-252.
10. Buzsáki, G. (2015). Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. Hippocampus, 25(10), 1073-1188. https://doi.org/10.1002/hipo.22488
11. Behrens, C. J., van den Boom, L. P., de Hoz, L., Friedman, A., & Heinemann, U. (2005). Induction of sharp wave–ripple complexes in vitro and reorganization of hippocampal networks. Nature Neuroscience, 8(11), 1560-1567. https://doi.org/10.1038/nn1571
12. Bragin, A., Engel, J. J., Wilson, C. L., Fried, I., & Buzsáki, G. (1999). High-frequency oscillations in human brain. Hippocampus, 9, 137-142.
13. Ylinen, A., Bragin, A., Nádasdy, Z., Jandó, G., Szabó, I., Sik, A., & Buzsáki, G. (1995). Sharp wave-associated high-frequency oscillation (200 Hz) in intact hippocampus: Network and intracellular mechanisms. The Journal of Neuroscience, 15(1), 30-46.
14. Ólafsdóttir, H. F., Bush, D., & Barry, C. (2018). The role of hippocampal replay in memory and planning. Current Biology, 28(1), R37-R50. https://doi.org/10.1016/j.cub.2017.10.073
15. Jadhav, S. P., Kemere, C., German, P. W., & Frank, L. M. (2012). Awake hippocampal sharp-wave ripples support spatial memory. Science, 336(6087), 1454-1458. https://doi.org/10.1126/science.121723 0
16. Chen, Z. S., & Wilson, M. A. (2023). How our understanding of memory replay evolves. Journal of Neurophysiology, 129(3), 552-580. https://doi.org/10.1152/jn.00454.2022
17. Diba, K., & Buzsáki, G. (2007). Forward and reverse hippocampal place-cell sequences during ripples. Nature Neuroscience, 10, 1241-1242. https://doi.org/10.1038/nn1961
18. Moser, M.-B., Rowland, D. C., & Moser, E. I. (2015). Place cells, grid cells, and memory. Cold Spring Harbor Perspectives in Biology, 7(2), a021808. https://doi.org/10.1101/cshperspect.a021808
19. Ambrose, R. E., Pfeiffer, B. E., & Foster, D. J. (2016). Reverse replay of hippocampal place cells is uniquely modulated by changing reward. Neuron, 91(5), 1124-1136. https://doi.org/10.1016/j.neuron.2016.07.047
20. Foster, D. J., & Wilson, M. A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature, 440(7084), 680-683. https://doi.org/10.1038/nature04587
21. Kumaran, D., Hassabis, D., & McClelland, J. L. (2016). What learning systems do intelligent agents need? Complementary learning systems theory updated. Trends in Cognitive Sciences, 20(7), 512-534. https://doi.org/10.1016/j.tics.2016.05.004
22. McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review, 102, 419-457. https://doi.org/10.1037/0033-295X.102.3.419
23. O'Doherty, J. P., Lee, S. W., & McNamee, D. (2015). The structure of reinforcement-learning mechanisms in the human brain. Current Opinion in Behavioral Sciences, 1, 94-100. https://doi.org/10.1016/j.cobeha.2014.10.004
24. Girardeau, G., Benchenane, K., Wiener, S. I., Buzsáki, G., & Zugaro, M. B. (2009). Selective suppression of hippocampal ripples impairs spatial memory. Nature Neuroscience, 12(10), 1222-1223. https://doi.org/10.1038/nn.2384
25. Zhang, Y., Cao, L., Varga, V., Jing, M., Karadas, M., Li, Y., & Buzsáki, G. (2021). Cholinergic suppression of hippocampal sharp-wave ripples impairs working memory. Proceedings of the National Academy of Sciences, 118(15), e2016432118. https://doi.org/10.1073/pnas.2016432118
26. Nour, M. M., Liu, Y., Arumuham, A., Kurth-Nelson, Z., & Dolan, R. J. (2021). Impaired neural replay of inferred relationships in schizophrenia. Cell, 184(16), 4315-4328.e17. https://doi.org/10.1016/j.cell.2021.06.012
27. Schultz, W. (2013). Updating dopamine reward signals. Current Opinion in Neurobiology, 23, 229-238. https://doi.org/10.1016/j.conb.2012.11.012
28. Schultz, W. (2016). Dopamine reward prediction error coding. Dialogues in Clinical Neuroscience, 18(1), 23-32. https://doi.org/10.31887/DCNS.2016.18.1/wschultz
29. Miyawaki, T., Norimoto, H., Ishikawa, T., Watanabe, Y., Matsuki, N., & Ikegaya, Y. (2014). Dopamine receptor activation reorganizes neuronal ensembles during hippocampal sharp waves in vitro. PLoS ONE, 9(8), https://doi.org/10.1371/journal.pone.0104438
30. Wilmerding, L. K., Yazdanbakhsh, A., & Hasselmo, M. E. (2022). Impact of optogenetic pulse design on CA3 learning and replay: A neural model. Cell Reports Methods, 2(5), https://doi.org/10.1016/j.crmeth.2022.100208