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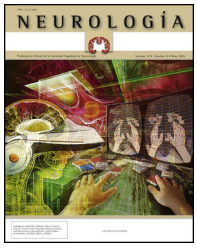

REVIEW ARTICLE

# Structural synaptic plasticity in the hippocampus induced by spatial experience and its implications in information processing☆

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**Abstract**
*Introduction:* Long-lasting memory formation requires that groups of neurons processing new information develop the ability to reproduce the patterns of neural activity acquired by experience.
*Development:* Changes in synaptic efficiency let neurons organise to form ensembles that repeat certain activity patterns again and again. Among other changes in synaptic plasticity, structural modifications tend to be long-lasting which suggests that they underlie long-term memory. There is a large body of evidence supporting that experience promotes changes in the synaptic structure, particularly in the hippocampus.
*Conclusion:* Structural changes to the hippocampus may be functionally implicated in stabilising acquired memories and encoding new information.


**PALABRAS CLAVE**
Plasticidad sináptica;
Hipocampo;
Experiencia espacial;
Memoria a largo plazo;
Ensambles neuronales;
Fibras musgosas

**Plasticidad sináptica estructural en el hipocampo inducida por la experiencia espacial y sus implicaciones en el procesamiento de información**

**Resumen**
*Introducción:* Para formar memorias perdurables, es necesario que los grupos de neuronas encargados de procesar la información que adquirimos desarrollen la capacidad de reproducir los patrones de actividad que se forman a través de la experiencia.
*Desarrollo:* Los cambios en la eficiencia sináptica permiten que las neuronas se organicen en «ensambles» y reproduzcan una y otra vez estos patrones de actividad. Entre los cambios en la eficiencia sináptica están las modificaciones en la estructura, las cuales tienden a perdurar

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por mucho tiempo y por ello se les vincula con la memoria a largo plazo. En la literatura existe amplia evidencia de que la experiencia promueve modificaciones en la estructura sináptica, particularmente en regiones como el hipocampo.
*Conclusión:* Las implicaciones funcionales de estos cambios en el hipocampo incluyen un posible papel en la estabilización de los recuerdos adquiridos y en la codificación de nueva información.


## Memory and its underlying neuronal mechanisms

One of the most remarkable features of humans and other animals is their ability to learn and remember. Humans can recognise stimuli encountered long before, such as the face of someone we met years ago. We can also establish long-lasting associations between stimuli such that we are consistently startled by car horns and are able to recognise our childhood surroundings and still find the small shop where we used to buy sweets.

The information that we obtain and keep in our memory is represented in the central nervous system by the coordinated activity of groups of neurons that develop the ability to repeat activity patterns acquired through experience. This idea shows that the information underlying cognitive processes, including memory, is represented in the central nervous system by groups of neurons called 'ensembles'.[1] This is known as population coding.[2] A graphic way to explain this concept is to compare neuronal units with the letters of the alphabet: it is not letters that convey information but rather the combination of letters and the order in which they are combined that creates meaningful words and sentences.

## Plasticity and neuronal ensembles

Renowned neuroanatomist Santiago Ramón y Cajal introduced the hypothesis that changes in synaptic connectivity of the CNS could provide the substrate for memory.[3] It was not until the middle of the past century that Donald Hebb (1945) formally introduced what is known today as 'Hebb's postulate': ''When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased''.

Lorente de Nó's concept of the 'reverberating circuits' became Hebb's empirical basis for explaining that the reverberation in 'neuronal ensembles' was the mechanism strengthening synaptic connections within the ensemble, which resulted in the ability to repeat activity patterns generated through experience. Ensembles can repeat activity patterns generated either without external stimuli (off-line activity patterns) or with partial stimulation using information related to the event that motivated memory creation (on-line activity patterns).

There are several types of changes in synaptic efficacy and some are more long-lasting than others. More specifically, changes in the structure of synaptic connections tend to last longer and may therefore be involved in long-term memory.[4]

## Where can population coding and ensemble dynamics be studied?

The hippocampus has shown itself to be the most suitable localisation for identifying and studying neuronal ensembles due to its anatomical location, the physiological characteristics of the neurons forming it, its plasticity, and its role in memory creation.

For more than 50 years now, we know that the hippocampus is essential for memory creation.[5] We also know, thanks to subsequent studies in animal models, that the hippocampus is involved in processing episodic information, which includes both spatial and temporal information.[6,7] The mechanisms underlying synaptic plasticity, such as long-term potentiation (LTP), can also be studied in the hippocampus using animal models. In this model of plasticity, postsynaptic response to low-frequency pulses increases in the long term after applying trains of high-frequency stimulation.[8,9] With this experimental model, synaptic efficacy has been shown to vary depending on the pathway's activity history, more specifically in the synapses of the stimulated pathway.[9,10] This finding, which served as the empirical basis for Hebb's postulate, was suggested as the mechanism underlying spatial memory consolidation in the hippocampus.[11] However, according to Hebb's original idea, the growth processes that may take place can be interpreted as changes in the structure of synaptic connections.

## Does experience change cerebral synaptic structure?

Empirical evidence of the changes in neuronal structure as a consequence of experience began to be published in the early 1960s, when Rosenzweig et al. introduced the paradigm of the 'enriched environment'.[12] Initially, these authors found that enriched environments had an effect on gross parameters, including brain weight and brain protein and nucleotide content.[12] In subsequent studies, environmental enrichment was proved to increase dendritic branching and the number of dendritic spines.[13] The key lesson is that since then, a connection between structural changes and improved learning skills has been described.

Greenough and Anderson[14] supported the idea that experience modifies the anatomical structure of neuronal networks. Using electron microscopy, these authors demonstrated that the size of synaptic contacts in the cerebellum and cerebral cortex would increase as a result of developing motor skills.

In the 1990s, Geinisman proved that LTP induction via perforant path stimulation increases the density of synaptic contacts in dentate granule cells.[15] In 1997, Escobar et al.[16] used Timm staining to observe that inducing mossy fibre LTP increases density of mossy fibre boutons in the stratum oriens of CA3. These studies demonstrated the high structural plasticity of the hippocampus. However, the question of whether those changes could occur in response to behaviour still remained unanswered.

## Experience-dependent structural synaptic plasticity in the hippocampus

In 1979, Altschuler provided the first evidence of structural synaptic plasticity in the hippocampus in response to differential experiences and training.[17] In that study, rats housed in enriched environments, including maze training, were compared to controls undergoing sessions on a motorised treadmill and to non-enriched controls. Electron microscopy displayed a marked increase in synaptic density in the area CA3.

In 1994, Moser et al.[18] compared dendritic spine density between rats exposed to complex environments promoting spatial learning and both control rats housed in pairs and control rats housed individually. These authors used confocal microscopy to analyse dendritic trees of CA1 pyramidal neurons after intracellular iontophoretic staining with Lucifer yellow and observed increased spine density in the group exposed to a complex environment. Likewise, the rats in this group performed better in the water maze task than controls. According to a subsequent study,[19] animal models exposed to complex environments displayed increased spine density in only one subgroup of dendritic segments in the stratum oriens of area CA1; this was not the case in isolated animal models, which showed low spine density compared to paired animals.

Using electron microscopy in 1997, Ruzakov et al.[20] found that training with a water maze promoted changes in the distribution of CA1 synaptic contacts; however, no changes in synaptic density were observed, probably due to the dendritic segments analysed.[19]

In the late 1990s, Ramírez-Amaya et al.[21] conducted a study using Timm staining and proved that spatial water maze overtraining resulted in increased density of mossy fibre boutons in the stratum oriens of area CA3. Electron microscopy confirmed the results and showed that these structural changes did not occur in animals exposed to stress or swimming.[21] Another study found that water maze training for 4 to 5 days led to improved performance on memory tests at 7 and 30 days after training compared to animals trained for 1 to 3 days.[22] Water maze performance was positively correlated with the density of mossy fibre boutons in the stratum oriens of area CA3, which suggested that increased mossy bouton density might be linked to spatial memory formation.[22]

Rekart et al.[23] used these findings to create a model to study structural synaptic plasticity in the hippocampus related to spatial learning. Using Timm staining and other markers such as synaptophystin,[24] these authors observed what they called 'mossy fibre terminal field expansion to the stratum oriens' in area CA3 in 2 rat strains. Long Evans rats[24] performed better on spatial tasks than Wistar rats, the strain that had been used previously.[21,22] This rat strain also showed increased mossy fibre terminal field innervation of the stratum oriens of CA3 before any spatial training.[24] Likewise, Long Evans rats displayed significant mossy fibre terminal field expansion to the stratum oriens of area CA3 24 hours after the last day of water maze training, while Wistar rats began showing expansion 7 days after acquisition.[25] The authors of these studies state that these structural changes may contribute to memory formation and facilitate subsequent execution of spatial navigation strategies.[24] According to Rekart et al.,[26] increased density of mossy fibre contacts in response to water maze training was not observed in mice. However, another research group using Timm staining found that water maze training in C57 mice increased mossy fibre synaptogenesis in the stratum oriens of CA3.[27] Behavioural factors are insufficient to explain the differences between results; the environments in which the animals were studied may constitute a possible explanation. As the rat develops, mossy fibres have been shown to expand to the stratum oriens in CA3 and subsequently retract; these processes are activity-dependent.[28] According to these findings, isolated animals show retraction of mossy fibre projections to the stratum oriens, while animals housed in an enriched environment may display preserved mossy fibre projections.

A larger area capturing Timm staining in the stratum oriens of animals undergoing water maze training has been regarded as indicative of synaptogenesis[21,22]; consequently, electron microscopy has shown that water maze training increases volume and complexity of thorny excrescences in apical dendrites of CA3 pyramidal cells,[29] where mossy fibres synapse. Using high-resolution confocal microscopy and a sophisticated image analysis procedure, Galimberti et al.[30] demonstrated that exposure to an enriched environment increases the volume and complexity of mossy fibre boutons that contact CA3 dendrites in the rat hippocampus.

Experimental evidence shows that changes in the density of mossy fibre synapses are induced only by hippocampus-dependent spatial tasks rather than navigation tasks independent of hippocampal function.[24,31]

There is no doubt that hippocampus-dependent spatial experience results in increased density and complexity of mossy fibre boutons contacting CA3 pyramidal cells in the hippocampus. Only one question remains to be answered, which we will address in the following section.

## What is the functional significance of experience?

Dentate granule cells give rise to mossy fibre axons; some of their terminals are large boutons with very

distinct characteristics which synapse with 'thorny excrescences' in CA3 pyramidal cell dendrites,[32,33] while filopodial extensions of the mossy terminals innervate inhibitory interneurons.[34] Mossy terminals co-release glutamate, zinc, and neuropeptides.[35] They have such a powerful input[36] that in 1987 McNaughton and Morris[37] considered them to be the triggering factor[38] for spike activity in CA3 pyramidal cells.

One old hypothesis is that the dentate gyrus orthogonalises information patterns coming from the entorhinal cortex.[39] Following this line of thought, during spatial information processing, 2% to 3% of neuronal units are recruited in the dentate gyrus,[40–42] which reflects a sparse coding that may enable optimal pattern separation, since recruiting the same ensemble in different representations is less probable.

CA3 axons, in addition to projecting afferences to CA1 pyramidal cells, also project recurrent collateral fibres contacting CA3 pyramidal cells, creating a fascinating proximal/distal and septal/temporal gradient; this is their salient feature.[43] It has been suggested that CA3 recurrent network operates as an auto-associative memory system,[37,44] which is essential to memory formation. The CA3 network accentuates the differences between representations, leading to excellent pattern separation, as occurs with the dentate gyrus. However, one characteristic exclusive to the CA3 network is its ability to perform pattern completion.[45] For this reason, the idea that CA3 is the main information storing mechanism of the hippocampus seems feasible.[46]

Input to CA3 pyramidal cells is diverse.[47] Although input from the dentate gyrus via the mossy fibres is extremely sparse,[48] it is crucial for CA3 function.[36] While only 10 to 18 mossy synapses contact each pyramidal cell, the number of synapses per pyramidal cell in weaker pathways, such as CA3 collaterals or pathways from CA1, runs to several thousands.[49]

CA3 pyramidal neurons receive information on the distance covered by the animal directly from the entorhinal cortex via the perforant path; the same information also travels to CA3 via the dentate gyrus. Thus, mossy fibres duplicate the information that CA3 cells receive from the entorhinal cortex. It has therefore been suggested that mossy fibres direct storage of new representations; the perforant path in turn transmits the cues that initiate retrieval of previously stored representations.[50] Thanks to its recurrent connections, CA3 compares patterns, engaging in statistical pattern completion to recognise familiar stimuli and separating them when representations are different.

Computational models propose that mossy fibres induce activity patterns that are relatively independent from any inputs received from CA3 and have a tendency to promote new information over activity patterns corresponding to the traces of previously acquired memories.[51] Thus, older memories prevail when activity of the recurrent collateral connections is more pronounced statistically. However, when a new activity pattern is stored, it is first recoded and transformed in the dentate gyrus network and then transmitted via the mossy fibres as an apparently random pattern arriving at the CA3 network.[50]

The function of mossy fibres is therefore to manage new information encoding rather than to retrieve previously stored information. This is apparently explained by the fact that mossy fibres, even when presenting associative plasticity, are unable to store information because their input is too sparse.[52]

Experimental evidence supports this hypothesis. Some studies have shown that reversible inactivation of CA3 terminals by injecting diethyldithiocarbamate while the water maze task is being trained has a negative impact on memory test results.[53] However, if terminals are inactivated immediately before memory retrieval, performance is not affected.[54,55] Inactivation of mossy fibres also affects the acquisition of recognition tasks.[56] This supports the idea that the dentate gyrus manages information storage in CA3, establishing not only new discrete patterns of activity[51] but also new, complete representations.[52]

On the other hand, sparse coding in the dentate gyrus and its sparse input to CA3 may be essential for storing new information in CA3. This postulate was analysed in a recent study[51] with a model using values of different functional characteristics of the dentate gyrus and CA3, assuming a fixed mossy fibre input strength. These values were calculated using experimental methods. Simulation of the computational model showed that the memory system has very sparse connectivity. However, these authors also observed that the high degree of sparseness leads to decreased information input, which means that the system will not function optimally if input provided by mossy projections is too reduced.[52] We should highlight that during the development of the rat hippocampus, mossy fibre input to CA3 projects profusely to the stratum oriens, but these fibres retract when stimulation is poor.[28] This means that mossy projections will be more abundant if the animal develops in an environment that stimulates hippocampal function, which in turn leads to optimal input enabling information storage in CA3. In contrast, when the environment is poor, mossy projections will be sparse and their input will consequently be suboptimal, which will reduce the ability of the hippocampus to encode new information.

This is consistent with studies reporting that genetically related animal species occupying different habitats present marked differences in density of CA3 infrapyramidal mossy fibre projections. These projections are associated with better performance on spatial tasks.[57–59] Likewise, density of mossy boutons in the infrapyramidal pathway in different rat strains predicts performance on different hippocampus-dependent tasks.[60] Pigmented mice (DBA is the oldest endogamic strain) presented lower densities of mossy contacts in the infrapyramidal pathway compared with C57 mice (black); consequently, mice of the latter strain performed better on hippocampus-dependent tasks.[61,62] Density of mossy projections of the infrapyramidal pathway shows a positive correlation with performance on the water maze task,[62,63] which is also correlated with other hippocampus-dependent tasks.[64]

In light of this evidence, we might conclude that formation of new mossy synapses in the stratum oriens of CA3 in response to experience[21,22] is a plastic change that improves encoding of new spatial memories. This is in line with rat studies showing that exposure to spatial tasks during adolescence increases density of mossy fibres in the stratum oriens of CA3 and improves performance of new spatial tasks in adulthood.[65,66] In conclusion, the role of mossy fibre synaptogenesis in response to spatial experience is to improve information encoding in the hippocampus.

However, returning to Hebb's postulates and assuming that structural synaptic plasticity is the most long-lasting,[4] the idea that these structural changes may also be involved in storing acquired memories is still valid, as has been previously suggested based on the positive correlation between density of mossy boutons in the stratum oriens of CA3 and performance on the water maze memory task.[22] Supporting this hypothesis, a recent study showed that behavioural experience promotes an increase in the density of connections between inhibitory cells and mossy fibres, which makes retrieval of acquired memories more precise.[67] We should highlight that the dentate granule cells connect with their postsynaptic targets by means of 3 types of terminals: large mossy terminals, which contact thorny excrescences of CA3 pyramidal cells and CA3 mossy cells in the hilar region; thin filopodial extensions of the mossy terminals, which mainly contact inhibitory interneurons; and en passant synaptic varicosities, which also contact interneurons.[34] Interestingly, density of interneuron contacts with filopodial extensions is 10 times higher than the density of contacts between large mossy terminals and pyramidal neurons.[34]

According to the study by Ruediger et al.,[67] one session of fear conditioning or several sessions of water maze learning during an 8-day period led to increased density of filopodial extensions compared to large mossy terminals. This was interpreted as an increase in feedforward inhibition. In line with this idea, water maze training was also observed to induce a significant decrease in the number of neurons involved in memory retrieval; activity was evaluated by measuring expression of an immediate early gene. These changes in the density of mossy contacts with inhibitory interneurons are temporarily correlated with the precision of a previously acquired memory.[67] These results support the idea that increased density of mossy contacts may be related to more precise information storage.

Although this hypothesis seems to contradict the idea that increased density of mossy contacts improves new information encoding, we feel that these 2 tasks are not necessarily mutually exclusive. While encoding of new information improves thanks to increased numbers of mossy fibres, it is possible that the circumstances in which off-line activity promotes plasticity[25] may also improve encoding of information acquired while performing the task inducing structural changes; this may not necessarily imply that mossy fibre synaptogenesis affects old memory retrieval.

Experimental evidence and the models that have been proposed lead us to support the idea that mossy fibre synaptogenesis in response to spatial learning promotes an overall change in hippocampal function. That being said, it is possible that synaptogenesis also influences other general mechanisms of hippocampal network function, such as statistical pattern completion.[68,69] This includes pattern separation and completion; the former allows the hippocampal network to optimally distinguish between different representations, and the latter process, to retrieve previously stored memories efficiently.[45,46,70]

Finally, in order to establish a connection between changes in mossy contact density and information storage we first need to determine whether those changes occur in the neurons involved in information processing.

Thorough experimental studies and greater attention to models of hippocampal function will be necessary to conclusively establish the functional role of mossy fibre synaptogenesis in response to experience. In any case, the current model of synaptic plasticity is extremely valuable and enables identification of mechanisms essential for understanding information processing in the CNS. In addition, this model will probably be useful for identifying neuronal units involved in long-term memory.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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## References

1. Hebb DO. The organization of behavior: a neuropsychological theory. Nueva York: John Wiley y Sons; 1945.
2. Sakurai Y. How do cell assemblies encode information in the brain. Neurosci Biobehav Rev. 1999;23:785—96.
3. Ramón y Cajal S. Histologie du système nerveux de l'homme et des vertébrés. Paris: A. Meloine Editor; 1909. Traducción del doctor L. Azoulay, 2 volúmenes; 1911.
4. Bailey CH, Kandel ER. Structural changes accompanying memory storage. Annu Rev Physiol. 1993;55:397—426.
5. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry. 1957;20:11—21.
6. Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS. The cognitive neuroscience of remote episodic, semantic and spatial memory. Curr Opin Neurobiol. 2006;16:179—90.
7. Eichembaum H, Fortin NJ. The neurobiology of memory based predictions. Philos Trans Roy Soc Lond. 2009;364:1183—91.
8. Bliss TVP, Lømo T. Plasticity in a monosynaptic cortical pathway. J Physiol (Lond). 1970;207:61.
9. Bliss TVP, Gardner-Medwin AR. Long-lasting potentiation of synaptic transmission in the dentate area of the unanaesthetized hippocampus following stimulation of the perforant path. J Physiol (Lond). 1973;232:357—437.
10. Watkins JC, Jane DE. The glutamate story. Br J Pharmacol. 2006;147:S100—8.
11. Morris RG, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature. 1986;319:774—6.
12. Rosenzweig MR, Krech D, Bennett EL, Diamond MC. Effects of environmental complexity and training on brain chemistry and anatomy: a replication and extension. J Comp Physiol Psychol. 1962;55:429—37.
13. Rosenzweig MR, Bennett EL. Psychobiology of plasticity: effects of training and experience on brain and behavior. Behav Brain Res. 1996;78:57—65.

14. Greenough WT, Anderson BJ. Cerebellar synaptic plasticity. Relation to learning versus neural activity. Ann N Y Acad Sci. 1991;627:231—47.
15. Geinisman Y. Structural synaptic modifications associated with hippocampal LTP and behavioral learning. Cereb Cortex. 2000;10:952—62.
16. Escobar ML, Barea-Rodríguez EJ, Derrick BE, Reyes JA, Martinez JL Jr. Opioid receptor modulation of mossy fiber synaptogenesis: independence from long-term potentiation. Brain Res. 1997;751:330—5.
17. Altschuler RA. Morphometry of the effect of increased experience and training on synaptic density in area CA3 of the rat hippocampus. J Histochem Cytochem. 1979;27:1548—50.
18. Moser MB, Trommald M, Andersen P. An increase in dendritic spine density on hippocampal CA1 pyramidal cells following spatial learning in adult rats suggests the formation of new synapses. Proc Natl Acad Sci U S A. 1994;91:12673—5.
19. Moser MB, Trommald M, Egeland T, Andersen P. Spatial training in a complex environment and isolation alter the spine distribution differently in rat CA1 pyramidal cells. J Comp Neurol. 1997;380:373—81.
20. Rusakov DA, Davies HA, Harrison E, Diana G, Richter-Levin G, Bliss TV, et al. Ultrastructural synaptic correlates of spatial learning in rat hippocampus. Neuroscience. 1997;80:69—77.
21. Ramírez-Amaya V, Escobar ML, Chao V, Bermúdez-Rattoni F. Synaptogenesis of mossy fibers induced by spatial water maze overtraining. Hippocampus. 1999;9:631—6.
22. Ramírez-Amaya V, Balderas I, Sandoval J, Escobar ML, Bermúdez-Rattoni F. Spatial long-term memory is related to mossy fiber synaptogenesis. J Neurosci. 2001;21:7340—8.
23. Rekart JL, Holahan MR, Routtenberg A. Presynaptic structural plasticity and long-lasting memory: focus on learning-induced redistribution of hippocampal mossy fibers. In: Bermúdez-Rattoni F, editor. Neural plasticity and memory: from genes to brain imaging. Boca Raton: CRC Press; 2007. Capítulo 5.
24. Holahan MR, Rekart JL, Sandoval J, Routtenberg A. Spatial learning induces presynaptic structural remodeling in the hippocampal mossy fiber system of two rat strains. Hippocampus. 2006;16:560—70.
25. Rekart JL, Sandoval CJ, Bermudez-Rattoni F, Routtenberg A. Remodeling of hippocampal mossy fibers is selectively induced seven days after the acquisition of a spatial but not a cued reference memory task. Learn Mem. 2007;14:416—21.
26. Rekart JL, Sandoval CJ, Routtenberg A. Learning-induced axonal remodeling: evolutionary divergence and conservation of two components of the mossy fiber system within Rodentia. Neurobiol Learn Mem. 2007;87:225—35.
27. Middei S, Vetere G, Sgobio C, Ammassari-Teule M. Landmark-based but not vestibular-based orientation elicits mossy fiber synaptogenesis in the mouse hippocampus. Neurobiol Learn Mem. 2007;87:174—80.
28. Holahan MR, Honegger KS, Routtenberg A. Expansion and retraction of hippocampal mossy fibers during postweaning development: strain-specific effects of NMDA receptor blockade. Hippocampus. 2007;17:58—67.
29. Stewart MG, Davies HA, Sandi C, Kraev IV, Rogachevsky VV, Peddie CJ, et al. Stress suppresses and learning induces plasticity in CA3 of rat hippocampus: a three-dimensional ultrastructural study of thorny excrescences and their postsynaptic densities. Neuroscience. 2005;131:43—54.
30. Galimberti I, Gogolla N, Alberi S, Santos AF, Muller D, Caroni P. Long-term rearrangements of hippocampal mossy fiber terminal connectivity in the adult regulated by experience. Neuron. 2006;50:749—63.
31. McGonigal R, Tabatadze N, Routtenberg A. Selective presynaptic terminal remodeling induced by spatial, but not cued, learning: a quantitative confocal study. Hippocampus. 2012;22:1242—55.
32. Amaral DG, Dent JA. Development of the mossy fibers of the dentate gyrus: I. A light and electron microscopic study of the mossy fibers and their expansions. J Comp Neurol. 1981;195:51—86.
33. Maccaferri G, Toth K, McBain CJ. Target-specific expression of presynaptic mossy fiber plasticity. Science. 1988;279:1368—70.
34. Acsády L, Kamondi A, Sík A, Freund T, Buzsáki G. GABAergic cells are the major postsynaptic targets of mossy fibers in the rat hippocampus. J Neurosci. 1998;18:3386—403.
35. Kobayashi K. Hippocampal mossy fiber synaptic transmission and its modulation. Vitam Horm. 2010;82:65—85.
36. Blackstad TW, Kjaerheim A. Special axo-dendritic synapses in the hippocampal cortex: electron and light microscopic studies on the layer of mossy fibers. J Comp Neurol. 1961;117:133—59.
37. McNaughton BL, Morris RGM. Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci. 1987;10:408—15.
38. Eccles JC. Synaptic and neuro-muscular transmission. Physiol Rev. 1937;17:538—55.
39. Sclabassi RJ, Eriksson JL, Port RL, Robinson GB, Berger TW. Nonlinear systems analysis of the hippocampal perforant path-dentate projection. I. Theoretical and interpretational considerations. J Neurophysiol. 1988;60:1066—76.
40. Ramírez-Amaya V, Vazdarjanova A, Mikhael D, Rosi S, Worley PF, Barnes CA. Spatial exploration-induced Arc mRNA and protein expression: evidence for selective, network-specific reactivation. J Neurosci. 2005;25:1761—8.
41. Chawla MK, Guzowski JF, Ramirez-Amaya V, Lipa P, Hoffman KL, Marriott LK, et al. Sparse environmentally selective expression of Arc RNA in the upper blade of the rodent fascia dentata by brief spatial experience. Hippocampus. 2005;15:579—86.
42. Leutgeb JK, Leutgeb S, Moser MB, Moser EI. Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science. 2007;315:961—6.
43. Ishizuka N, Cowan WM, Amaral DG. A quantitative analysis of the dendritic organization of pyramidal cells in the rat hippocampus. J Comp Neurol. 1995;362:17—45.
44. Rolls ET. Functions of neuronal networks in the hippocampus and neocortex in memory. In: Byrne JH, Berry WO, editors. Neural models of plasticity: experimental and theoretical approaches. San Diego: Academic Press; 1989. p. 240—65.
45. Guzowski JF, Knierim JJ, Moser EI. Ensemble dynamics of hippocampal regions CA3 and CA1. Neuron. 2004;44:581—4.
46. Leutgeb S, Leutgeb JK. Pattern separation, pattern completion, and new neuronal codes within a continuous CA3 map. Learn Mem. 2007;14:745—57.
47. Witter MP. Intrinsic and extrinsic wiring of CA3: indications for connectional heterogeneity. Learn Mem. 2007;14:705—13.
48. Claiborne BJ, Amaral DG, Cowan WM. A light and electron microscopic analysis of the mossy fibers of the rat dentate gyrus. J Comp Neurol. 1986;246:435—58.
49. Amaral DG, Ishizuka N, Claiborne B. Neurons, numbers and the hippocacampal network. Progr Brain Res. 1990;83:1—11.
50. Treves A, Tashiro A, Witter ME, Moser EI. What is the mammalian dentate gyrus good for. Neuroscience. 2008;154:1155—72.
51. Treves A, Rolls ET. Computational constraints suggest the need for two distinct input systems to the hippocampal CA3 network. Hippocampus. 1992;2:189—99.
52. Cerasti E, Treves A. How informative are spatial CA3 representations established by the dentate gyrus? PLoS Comput Biol. 2010;6:e1000759.
53. Lassalle JM, Bataille T, Halley H. Reversible inactivation of the hippocampal mossy fiber synapses in mice impairs spatial learning, but neither consolidation nor memory retrieval, in the Morris navigation task. Neurobiol Learn Mem. 2000;73:243—57.
54. Lee I, Kesner RP. Encoding versus retrieval of spatial memory: Double dissociation between the dentate gyrus and the

perforant path inputs into CA3 in the dorsal hippocampus. Hippocampus. 2004;14:66—76.
55. Florian C, Roullet P. Hippocampal CA3-region is crucial for acquisition and memory consolidation in Morris water maze task in mice. Behav Brain Res. 2004;154:365—74.
56. Stupien G, Florian C, Roullet P. Involvement of the hippocampal CA3-region in acquisition and in memory consolidation of spatial but not in object information in mice. Neurobiol Learn Mem. 2003;80:32—41.
57. Schwegler H, Mueller GG, Crusio WE, Szemes L, Seress L. Hippocampal morphology and spatially related behavior in Long-Evans and CFY rats. Hippocampus. 1993;3:1—7.
58. Bernasconi-Guastalla S, Wolfer DP, Lipp HP. Hippocampal mossy fibers and swimming navigation in mice: correlations with size and left-right asymmetries. Hippocampus. 1994;4:53—63.
59. Pleskacheva MG, Wolfer DP, Kupriyanova IF, Nikolenko DL, Scheffrahn H, Dell'Omo G, et al. Hippocampal mossy fibers and swimming navigation learning in two vole species occupying different habitats. Hippocampus. 2000;10:17—30.
60. Schwegler H, Crusio WE. Correlations between radial-maze learning and structural variations of septum and hippocampus in rodents. Behav Brain Res. 1995;67:29—41.
61. Crusio WE, Schwegler H, Lipp HP. Radial-maze performance and structural variation of the hippocampus in mice: a correlation with mossy fiber distribution. Brain Res. 1987;425:182—5.
62. Schöpke R, Wolfer DP, Lipp HP, Leisinger-Trigona MC. Swimming navigation and structural variations of the infrapyramidal mossy fibers in the hippocampus of the mouse. Hippocampus. 1991;1:315—28.
63. Prior H, Schwegler H, Ducker G. Dissociation of spatial reference memory, spatial working memory, and hippocampal mossy fiber distribution in two rat strains differing in emotionality. Behav Brain Res. 1997;87:183—94.
64. Lipp HP, Schwegler H, Heimrich B, Driscoll P. Infrapyramidal mossy fibers and two-way avoidance learning: developmental modification of hippocampal circuitry and adult behavior of rats and mice. J Neurosci. 1988;8:1905—21.
65. Keeley RJ, Wartman BC, Häusler AN, Holahan MR. Effect of juvenile pretraining on adolescent structural hippocampal attributes as a substrate for enhanced spatial performance. Learn Mem. 2010;17:344—54.
66. Wartman BC, Gervais NJ, Smith C, Comba R, Mumby DG, Holahan MR. Enhanced adolescent learning and hippocampal axonal projections following preadolescent spatial exposure to a water or dry maze. Brain Res. 2012;1475:37—48.
67. Ruediger S, Vittori C, Bednarek E, Genoud C, Strata P, Sacchetti B, et al. Learning-related feedforward inhibitory connectivity growth required for memory precision. Nature. 2011;473:514—8.
68. Marr D. A theory of cerebellar cortex. J Physiol (Lond). 1969;202:437—70.
69. Marr D. Simple memory: a theory for archicortex. Philos Trans R Soc Lond B: Biol Sci. 1971;262:23—81.
70. Leutgeb JK, Leutgeb S, Treves A, Meyer R, Barnes CA, McNaughton BL, et al. Progressive transformation of hippocampal neuronal representations in morphed'' environments. Neuron. 2005;48:345—58.