NMDA RECEPTORS, PLACE CELLS AND HIPPOCAMPAL SPATIAL MEMORY

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N-methyl-D-aspartate receptors (NMDARs) in the rodent hippocampus have been shown to be essential for spatial learning and memory, and for the induction of long-term synaptic plasticity at various hippocampal synapses. In this review, we examine the evidence concerning the role of NMDARs in hippocampal memory processes, with an emphasis on the function of NMDARs in area CA1 of the hippocampus in memory acquisition, and the unique role of NMDARs in area CA3 in the rapid acquisition and associative retrieval of spatial information. Finally, we discuss the data that have emerged from *in vivo* hippocampal recording studies that indicate that the activity of hippocampal place cells during behaviour is an expression of a memory trace.

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Scoville and Milner's study in the 1950s of patient H.M., who had undergone a bilateral resection of the hippocampus and associated cortical areas, indicated that these parts of the brain, collectively called the medial temporal lobe (MTL), are crucial in the formation of declarative memory (memory of facts and events)[1]. Subsequent studies on H.M. and other patients, as well as studies on animal models, have enriched our knowledge about the roles of the MTL and its components in declarative memory[2–5]. It has become clear that the hippocampus has an essential role in, among other types of memory, spatial memory — a type of declarative memory that is concerned with spatial locations[6,7]. In 1971, O'Keefe and Dostrovsky discovered 'place cells'[8] (BOX 1), showing that space can be encoded in the firing pattern of the hippocampus.

Concurrent with these studies, Bliss and Lømo discovered that high-frequency stimulation of the hippocampal input fibres can result in long-lasting enhancement of transmission efficacy at downstream synapses[9]. This discovery of long-term potentiation (LTP) provided the first experimental support for Hebb's theory on the neural representation of memory[10]. Hippocampal LTP has subsequently been subjected to extensive study as a candidate mechanism for learning and memory. The induction of LTP in area CA1 of the hippocampus is blocked by D(–)-2-amino-5-phosphonovaleric acid (AP5), an antagonist of the

NMDA subset of glutamate receptors[11]. The NMDAR possesses a voltage-dependent magnesium block, high calcium permeability and slow activation and deactivation kinetics[12–15]. Consequently, the NMDAR can be opened by glutamate only when the postsynaptic neuron is depolarized, thereby allowing the receptor to function as a detector and integrator of coincident activity at the synapse. The finding that the induction of hippocampal LTP depends on the activation of NMDARs further strengthened the link between LTP and Hebb's synaptic hypothesis for memory storage, in which modifications of synaptic efficacy by coincident input was the central theme. The demonstration that infusion of AP5 into the ventricles of rats caused an impairment in spatial learning indicated that NMDAR activation might be crucial for this type of memory[16].

Studies on the role of NMDARs in memory intensified when the genes encoding the receptor were cloned during the early 1990s[17], allowing the NMDAR subunits to be identified and characterized. Among the seven identified subunits (NR1, NR2A–D, and NR3A and B), the NR1 subunit is the only one that is indispensable for the formation of a functional receptor; its elimination would abolish all functional NMDARs in a cell[18,19]. As AP5 inhibits LTP induction in hippocampal slices and spatial memory in intact animals, it might be expected that elimination of the *NR1* gene would lead to similar physiological and behavioural deficits.

Box 1 | **Place cells**

In 1971, O'Keefe and Dostrovsky found that single hippocampal neurons increased their firing rate whenever a rat traversed a particular region of a chamber [8]. When they recorded extracellular action potentials from the hippocampus of freely moving rats, some hippocampal pyramidal cells demonstrated firing patterns that seemed to depend on the animal's location in the environment. When the rat left the 'place' that was encoded by a given cell, the cell fell almost silent. In an open field, the firing rate was also independent of the direction in which the animal entered the area and the direction that it was facing. The firing of each cell seemed to indicate a specific location in the environment of the rat; so these cells are called 'place cells'.

Panel a represents the place-specific firing properties of hippocampal pyramidal cells as a rodent runs down a linear track. Each cell fires only on a specific region of the track. A common method of representing these place fields (right) is a firing rate map — a top-down view of the environment

with areas of high firing rate coloured red and yellow and areas with no firing coloured blue. Panel b shows 80 firing rate maps of cells simultaneously recorded from area CA1 of a rat exploring a square arena. Most cells are silent as the rat forages, with only about 30% of the pyramidal cells active in this environment. The six cells that fire throughout the environment are thought to be interneurons [125].

Since 1971, neuroscientists have conducted hundreds of studies to characterize the properties and dependencies of place-cell activity [153–156]. Studies using freely behaving rats have shown that pyramidal cells show stable, long-lasting, environmentally specific place fields, with between 30% and 50% of the CA1 cell layer showing place-specific activity in any given environment [125,157,158]. When an animal is introduced to a novel environment, these place cells form rapidly, usually within five minutes, and are maintained robustly [125]. The relative locations of these place-receptive fields change in different environments, with no apparent topographical relationship to cell position, so new place fields must be learned in each environment [159].

More recent studies have shown that any given place is encoded not by the activity of single neurons, but instead by a population of simultaneously active cells [125]. Parameters such as the coefficient of variance, a measure of temporal correlation, allow the spatial coding properties of an ensemble of cells to be assessed. For example, both pairs and sequences of cells that were active during behaviour, owing to close proximity of their place fields, tend to be reactivated in a coordinated manner during periods of slow-wave and rapid eye movement (REM) sleep following behaviour [124,127,128,132,133]. This increase in correlated activity during sleep might reflect cellular and network learning mechanisms.

Place cells have been best characterized in area CA1 of the rat hippocampus, but they have also been studied in the other hippocampal subfields and in the entorhinal cortex [74,75]. The recording and analysis of fields in the genetically modified mouse has also been applied to understanding the hippocampal code for space. Panel b reproduced, with permission, from REF. 125 © (1993) American Association for the Advancement of Science.
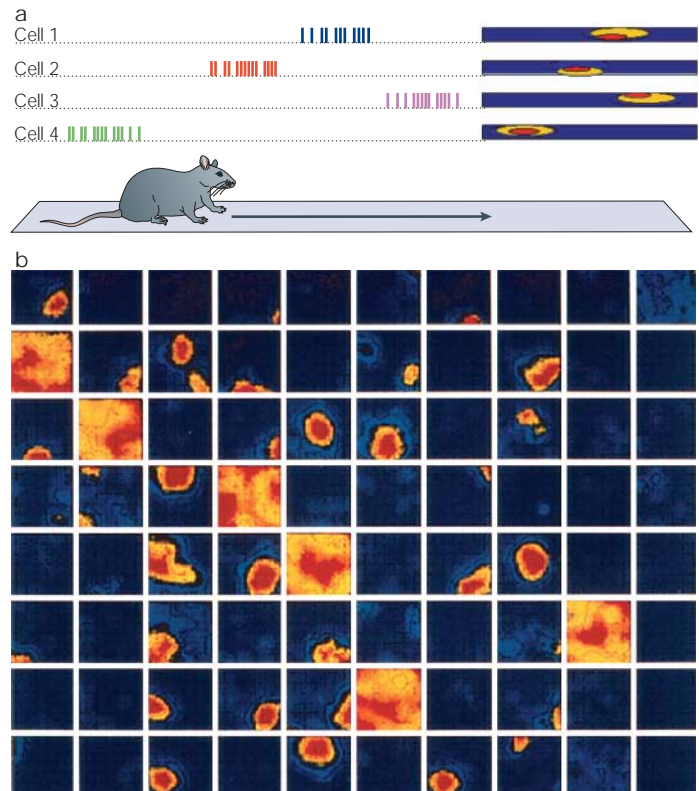
However, *NR1*-knockout mice do not survive for more than a day after birth because of the role of this receptor in the midbrain for breathing [20,21]. This illustrates the need for spatial and temporal restriction of genetic interventions for the effective study of memory and other cognitive phenomena.

The role of the NMDAR in spatial representation and spatial memory in the hippocampus must be considered and studied in the context of hippocampal anatomy. As in humans and non-human primates, the rodent

hippocampus can be divided into the dentate gyrus (DG), area CA3 and area CA1 (FIG. 1). In the main excitatory pathway, the trisynaptic circuit, information flows from layer II stellate cells of the entorhinal cortex (EC) to granule cells in the DG though the perforant path, from the granule cells to the CA3 pyramidal cells through the mossy fibres, from the CA3 pyramidal cells to the CA1 pyramidal cells though the Schaffer collaterals, and finally from the CA1 pyramidal cells to cells in the deep layers of the EC. In addition, layer II stellate cells and layer III
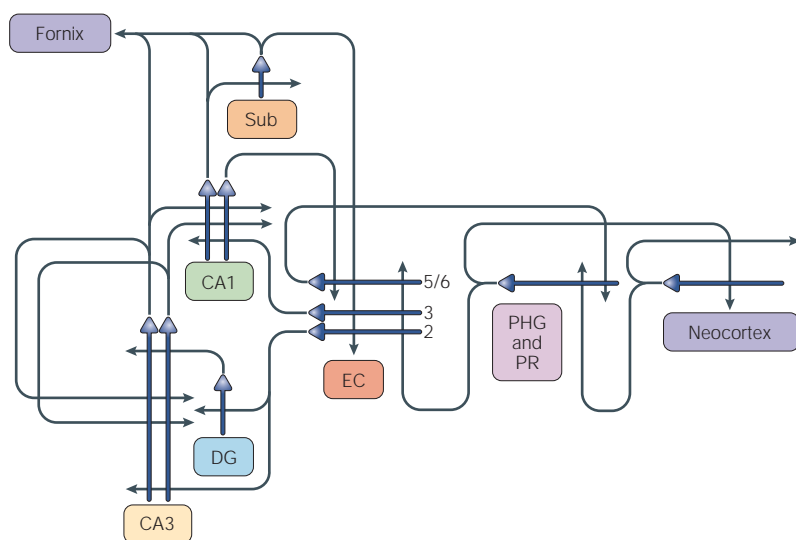
Figure 1 | **Connections in the corticohippocampal network**. Sensory information from the cerebral association neocortex (neocortex) arrives at the superficial layers of the entorhinal cortex (EC) by way of the parahippocampal gyrus (PHG) and/or perirhinal cortex (PR). From the EC, the information is routed into the hippocampus. The main subfields of the hippocampus and the connections among them and with the superficial layers of the EC are described in the text. CA1 sends axons to both subcortical areas and the deep layers of the EC, either directly or through the subiculum (Sub). The corticohippocampal network is then completed, with the information from CA1 being sent back to cerebral association cortex through the PHG and/or PR. Thick lines below or to the right of cell bodies (triangles) represent dendrites. Numbers refer to cortical layers. DG, dentate gyrus.

pyramidal cells of the EC send axons directly to area CA3 (through the perforant path) and area CA1 (through the temporoammonic pathway), respectively[22]. Furthermore, CA3 pyramidal cells are interconnected by recurrent collaterals that run both ipsilaterally and contralaterally. Among the three types of excitatory input that CA3 pyramidal cells receive, these recurrent collateral inputs are the most numerous (about 12,000 per pyramidal cell in the rat), whereas the perforant path and mossy fibre inputs provide about 4,000 and 50 inputs per cell, respectively. Owing to the recurrent collaterals, the connectivity among CA3 pyramidal cells is robust; a given cell is directly connected with at least 2% of the other cells[23,24].

A number of theoretical studies have proposed a distinct mnemonic role for each of the hippocampal subfields and inputs[25–28]. For instance, it has been postulated that the recurrent network in CA3 is crucial for the storage of associative memory and its recall by 'pattern completion', whereas the DG is involved in the separation of similar memories ('pattern separation'). It has also been suggested that the CA1 network might be instrumental in recognizing the novelty or familiarity of an object or context[29]. However, it is only recently that some of these hypotheses have been tested empirically.

Memory acquisition
Early support for the link among NMDAR activity, hippocampal LTP and learning and memory came from Morris and colleagues. They developed a hippocampus-dependent behavioural task for rats using a circular pool filled with opaque water in which an escape platform was hidden at a fixed location below the surface

(the hidden-platform version of the Morris water maze (MWM) task[6,30]). Initially, rats that are placed in the pool find the escape platform by random navigation. However, over repeated training trials, they slowly learn the location using objects outside the maze as cues and eventually swim nearly straight to the platform. Blockade of NMDARs by intraventricular infusion of AP5 resulted in an impairment of spatial learning on the hidden-platform MWM task, but not if the platform was visible[16]. The estimated extracellular concentrations of AP5 in the hippocampus that caused the spatial learning impairment were comparable to those that blocked LTP *in vivo* at synapses between the perforant path and the DG[31]. Intrahippocampal injection of AP5 resulted in similar behavioural deficits[32]. By contrast, intrahippocampal administration of an AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)/kainate receptor antagonist, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) or LY326325, resulted in a severe memory deficit with either the hidden or the visible platform[33].

These results indicated that hippocampal NMDAR activity and NMDAR-dependent plasticity are crucial for spatial learning. However, NMDAR antagonists could have nonspecific effects on neural activity. For instance, AP5 can cause a reduction in hippocampal excitability[34,35]. Furthermore, intraventricular infusion of AP5 often results in diffusion of the drug to areas outside the hippocampus, which could impair both sensory and motor function[36,37]. The possibility that unintended effects of AP5 contributed to the observed learning deficits could not be excluded.

A complementary approach was provided by genetically engineered mice, in which deletion of the *NR1* gene was restricted to particular cell types using the phage P1-derived, Cre/*loxP* recombination system[38,39] (BOX 2). Tsien *et al.* created a mouse strain in which the *NR1* gene was postnatally knocked out predominantly in CA1 pyramidal cells (referred to as CA1-*NR1*-knockout mice)[40]. This mouse strain had apparently normal growth and was fertile.

CA1-*NR1*-knockout mice showed severely impaired spatial learning in the hidden-platform MWM, but performed normally when the platform was visible[40]. A possible explanation for this deficit came from *in vivo* recordings of CA1 pyramidal cells[41]. Place cells that were recorded while CA1-*NR1*-knockout mice traversed a linear track had altered single-cell and ensemble properties. The individual fields were larger and less structured than normal, and the coefficient of variance — a measure of the temporal coordination of the firing of cells with overlapping place fields — was greatly reduced, indicating a loss of coherent spatial representation at the ensemble level. Furthermore, the *in vitro* induction of LTP was specifically blocked at the Schaffer collateral (SC)–CA1 synapses. In these mice, NR1 deletion is delayed until about 4 weeks after birth and is restricted to CA1 pyramidal cells until about 2 months of age[42]. So, it is unlikely that the behavioural impairment is the result of undetected developmental abnormalities, and although a small percentage of the animals that were used for behavioural and physiological characterization might

Box 2 | **Conditional genetic manipulations**

Conditional genetic techniques have been used in rodents to confine the manipulation of a gene to a particular tissue or cell type and/or a desired time point, allowing spatial and temporal control of a gene of interest *in vivo*. The Cre/*loxP* system is the most widely used technique for manipulating the mouse genome[160,161]. Cre is a site-specific DNA recombinase derived from the P1 bacteriophage that recognizes 34 base-pair sequences termed *loxP* sites. Cre catalyses the deletion of a segment of DNA that is flanked by a pair of these *loxP* sites (*floxed*), resulting in a 'knockout' of the gene of interest (a). To create mice in which a gene knockout is restricted to a brain subregion, two transgenic mouse lines are created and intercrossed: one line is composed of mice in which a pair of *loxP* sites are introduced by homologous recombination into the gene to be knocked out and the other line comprises transgenic mice in which the expression of the Cre recombinase is driven by a tissue-specific or cell-type-specific transcriptional promoter (a). When these are bred together, the restricted expression of the recombinase leads to a specific deletion of the *floxed* gene only in the tissue of interest. The use of promoters that are active only in the adult minimizes the developmental and compensatory effects that are often seen in conventional knockout mice[162–164]. Panel b shows *in situ* hybridization using a probe that is specific for the NR1 transcript. In the absence of the recombinase, the transcript is expressed throughout the brain (left); however, Cre expression leads to a CA1-specific deletion of the gene (arrow, right).

To endow temporal specificity to a genetic alteration, there are various techniques for creating mice with inducible expression of genes[165]. In the nervous system, the most widely used inducible approach is the tetracycline-dependent regulatory system[166]. The tetracycline transactivator (tTA), a fusion of the tet repressor protein of *Escherichia coli* and the carboxy (C)-terminal domain of the herpes simplex virus VP16 protein, is used as a transcriptional ON/OFF switch to drive the expression of a gene of interest[109]. Like the Cre/*loxP* system, the tTA system requires the use of two lines of transgenic mice — mice in which the expression of the tTA protein is driven by a tissue or cell-type-specific promoter, and mice in which a gene of interest is placed downstream of a tandem array of the tet operator (tetO), along with a minimal promoter (c). In the original and most frequently used version of this system, the tTA protein binds to the tetO sequence and induces transcription. However, when the inducer (tetracycline) is present, it binds to tTA and prevents it from binding to tetO, which halts transcription. Many laboratories have now reported the successful application of the tTA system to neuroscience, observing that removal of tetracycline from the animals' food or water leads to robust expression of the exogenous transgenic protein in the brain[167–169]. The application and combination of spatial restriction by the Cre/*loxP* system and of temporal control by the tTA system has allowed the generation of more precise reagents for the study of systems neuroscience.
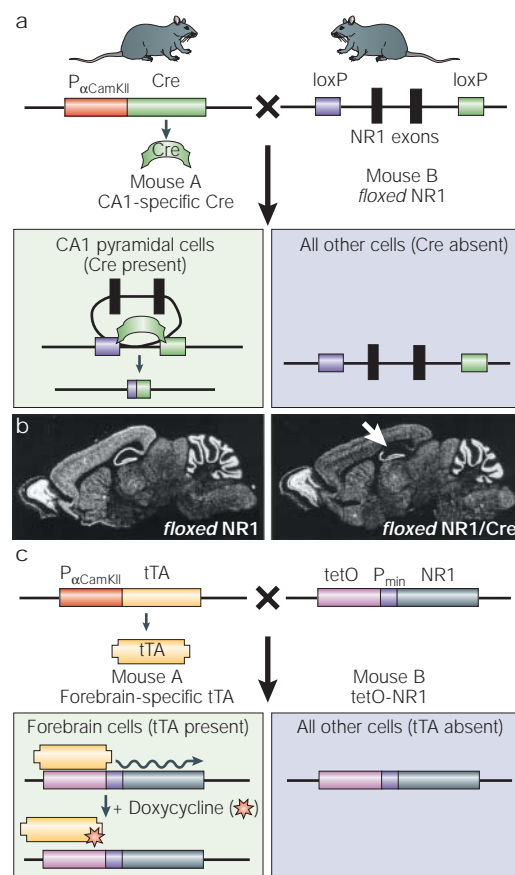
FEAR CONDITIONING
A form of Pavlovian (classical) conditioning in which the animal learns that an innocuous stimulus (for example, an auditory tone — the conditioned stimulus or CS), reliably predicts the occurrence of a noxious stimulus (for example, foot shock — the unconditioned stimulus or US) following their repeated paired presentation. As a result of this procedure, presentation of the CS alone elicits conditioned fear responses previously associated with the noxious stimulus only.

TRANSVERSE PATTERN LEARNING
A task in which animals must encode overlapping relationships between cues. A typical stimulus set is A+B–; B+C–; C+A–, where + signifies which cue is rewarded in each configuration.

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have harboured a more widespread deletion of the *NR1* gene, most of the analysis was done with young mice in which the knockout was CA1-specific. In addition, the lack of NR1 deletion in the neocortex alleviated the main concern that accompanied the AP5 administration experiments. The combination of pharmacological and genetic studies has therefore provided strong evidence that NMDAR activity and NMDAR-dependent synaptic plasticity in the hippocampus are crucial for spatial learning and for the proper formation and coordination of CA1 place fields. The importance of CA1 NMDARs in the acquisition of hippocampus-dependent memory was subsequently extended to various non-spatial tasks, including recognition of novel objects, contextual FEAR CONDITIONING, trace fear

conditioning and TRANSVERSE PATTERN LEARNING[43–45]. However, we focus on spatial memory in this review, to compare and contrast the molecular genetic, behavioural, pharmacological and electrophysiological data that support our evaluation of NMDARs in hippocampal function.

Pretraining spares spatial learning. Despite the evidence outlined above, some subsequent studies called into question the role of NMDAR-dependent plasticity in spatial learning. Most strikingly, NMDAR antagonists failed to disrupt new spatial learning in the hidden-platform MWM task in rats that had received spatial[46] or non-spatial[47] pretraining in a different environment. The hippocampus was still needed for new spatial learning by the pretrained animals[46]. Pretraining also protects
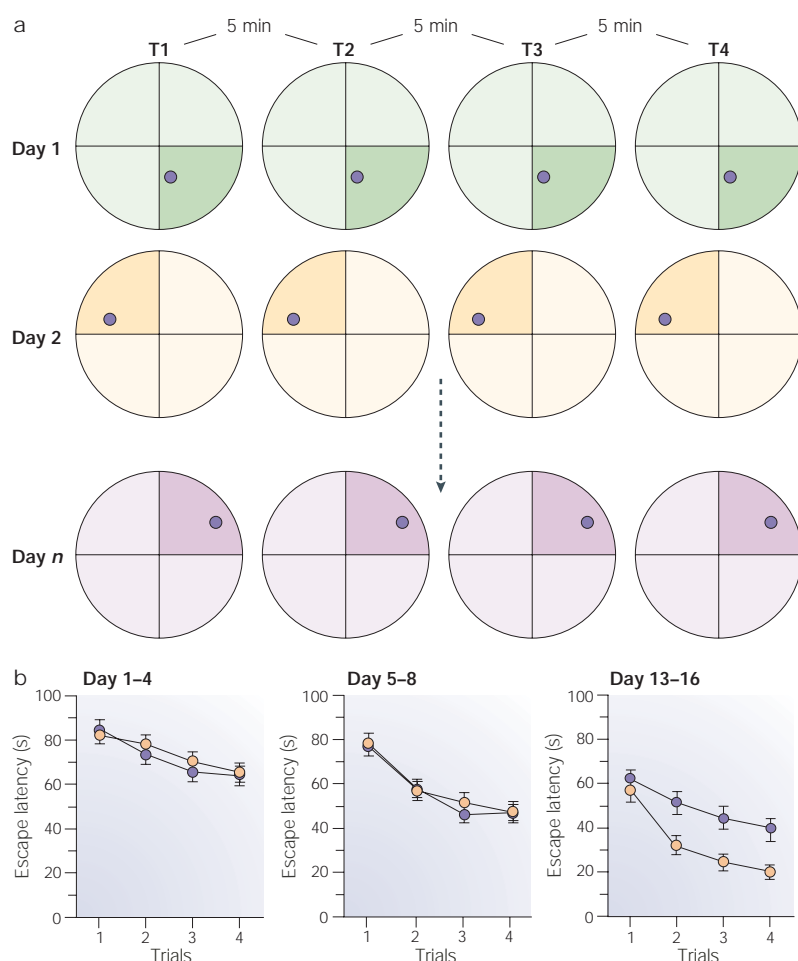
Figure 2 | **CA3-*NR1*-knockout mice are impaired in delayed matching-to-place task in water maze**. **a** | Animals are given four trials (T1–T4) per day with a 5-min intertrial interval. During a given day the hidden platform remains at a fixed location, but between days, the platform is moved to novel locations. **b** | Performance is averaged across 16-trial blocks during training (day 1–4, 5–8, 9–12 and 13–16). The escape latency is relatively long on trial 1 each day because the animal will have to conduct a random search for the novel platform location, but it is reduced gradually on trials 2, 3 and 4. Up to and including day 12, there were no differences in the escape latencies between CA3-*NR1*-knockout mice and their control littermates, indicating that the mutants are not impaired in the 'rule learning' phase of the task. On days 13–16, however, the mutants exhibited latency deficits in trials 2–4. These results indicate that the mutants are impaired in the rapid encoding of novel spatial information[69].

Spatial delayed matching-to-place task. One clue came from the effects of AP5 in the delayed matching-to-place (DMP) version of the MWM[50] (FIG. 2). In this task, the location of the platform was altered daily in a pseudo-random fashion. On each day, four trials were given with intertrial intervals of 20 min or 2 h. The mean latencies to find the platform are relatively long for the first trial of a day, because the animals are unaware of the novel location of the platform, but for untreated rats they are significantly shortened in the second trial owing to the memory that was acquired earlier that day. However, infusion of AP5 into the hippocampus substantially reduced the latency savings on the second trial. Pretraining over 9 days with a novel platform location each day did not alter the NMDAR-dependency of this one-trial spatial learning. This is in contrast to the results of the MWM task in which pretraining absolved the need for NMDAR function in new spatial learning. What features of the two water maze tasks resulted in this difference?

In the DMP task, the animals have presumably familiarized themselves with both the task rules and the environment by the end of the pretraining session. To reduce the latency on the second trial of a test day, the animal must depend on information about the platform location that it obtained during the first trial of the day. The animals must distinguish the most recent (today's) platform location from those experienced in the preceding days. These requirements are reminiscent of those for human episodic memory[51,52]. Although it has been forcefully argued by some that episodic memory is beyond the capability of non-human animals[53], recent studies on food-caching and recovery in scrub jays[54] indicate that animals can memorize 'what', 'where' and 'when' information, a hallmark of episodic memory[55]. Hippocampal NMDARs might be needed for this episodic aspect of spatial learning[56].

In contrast to the DMP task, which demands rapid acquisition of the memory for the novel platform location in one trial, the hidden-platform MWM task allows slow acquisition of the memory of the fixed platform location, and its performance can be improved incrementally throughout multiple trials. During the early stages of training, animals probably rely on single-trial memory, sometimes referred to as episodic information, for the performance improvement as in the DMP task, but as the training advances they might gradually form more trial-independent spatial memory. We suggest that hippocampal NMDARs are required in the early, trial-dependent phase of the task, but not in the later, trial-independent phase. When animals undergo extensive pretraining on this task, even in a distinct environment, it might minimize the trial-dependent phase of new spatial learning and thereby render it insensitive to AP5 blockade in the hippocampus. A similar idea has been suggested by Moser and Moser[57]. The idea could be tested by varying the timing of AP5 injection during training, or by generating and analysing mice in which hippocampus-targeted inhibition of NR1 function is temporally controlled.

STEP-DOWN INHIBITORY AVOIDANCE TASK
A form of conditioning in which a rat is placed on a platform and receives a shock when it steps off the platform. Memory for the shock is measured as an increased latency to step off the platform on subsequent trials.

learning on a STEP-DOWN INHIBITORY AVOIDANCE TASK in rats that have received an intrahippocampal infusion of AP5 (REF. 48). The NMDAR dispensability that is induced by pretraining seems to reflect the complexity of the learning associated with these behavioural tasks. In the hidden-platform MWM task, animals must learn various behavioural strategies and rules, including swimming away from the side walls to find a platform, discovering the hidden platform, and climbing and staying on the platform, before they can learn the location of the platform allocentrically using the extra maze cues. One possible explanation for the lack of NMDAR-dependency in pretrained animals is that the strategy or rule learning, but not the spatial learning *per se*, requires NMDAR function. However, subsequent work did not support this hypothesis[49]. So why does the MWM task depend on hippocampal NMDARs?
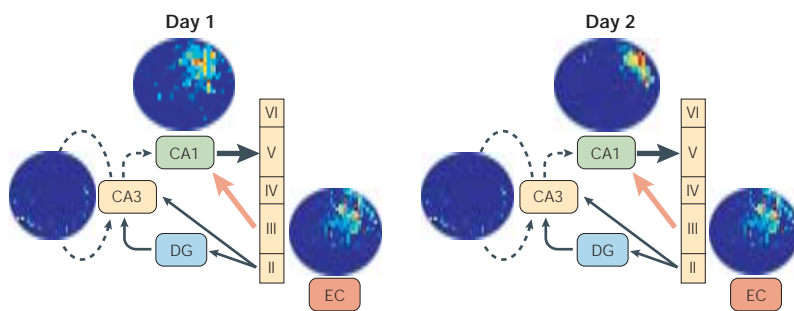
Day 1   **Day 2**

Figure 3 | **Impaired rapid formation of CA1 place fields as a consequence of CA3 NMDAR knockout.** On the first day of exploration in a novel environment, the spatial tuning of CA1 place cells is compromised (that is, the place fields are enlarged) in CA3-*NR1*-knockout mice. It is proposed that these CA1 responses reflect equally poorly tuned entorhinal cortex (EC) place-cell activities. In normal animals, the poor spatial tuning will be quickly remedied within a few minutes by the highly tuned drive from CA3 (not shown). But in the mutants, owing to the lack of NMDARs (*N*-methyl-D-aspartate receptors), CA3 cells fail to provide such a drive and therefore the spatially poorly tuned CA1 responses continue for at least 1 hour. However, by the time the mutants are re-exposed to the same environment on the second day, a slow spatial refinement of CA1 place-cell activities has been implemented off-line through an unknown mechanism. DG, dentate gyrus.

CA3 NMDARs and one-trial learning. The CA3 subfield of the hippocampus has a robust recurrent network, with pyramidal cells receiving synaptic contacts from ~2% of other CA3 pyramidal cells[58,59] (FIG. 1). NMDAR-dependent LTP has also been demonstrated at the synapses of recurrent collaterals in CA3 as well as at perforant path–CA3 synapses, whereas the plasticity at dentate mossy fibre–CA3 synapses is NMDAR-independent[60–64]. Marr and others have suggested that recurrent networks with modifiable synaptic strength could support the rapid acquisition of memories of a one-time experience[28,65,66]. Although Steele and Morris's pharmacological blockade experiment indicated that hippocampal NMDARs are involved in delay-dependent rapid acquisition of one-time experience memory, a more targeted intervention method would be needed to identify specific hippocampal subfields and circuitries in which NMDARs play this crucial part.

Lee and Kesner[67] attempted to inject AP5 bilaterally, primarily into CA3, CA1 or the DG in rats that had been trained on a radial eight-arm maze using a delayed non-matching-to-place experiment, and tested whether the rats chose the previously unvisited arm to obtain a reward using spatial cues. Rats that had been treated with AP5 directed towards CA3 were impaired at carrying out this task in a novel environment, consistent with the hypothesis that NMDARs in CA3 are more important than those in CA1 or DG for the acquisition of spatial 'working memory' (equivalent to episodic-like memory) in a novel environment.

Nakazawa *et al.* generated a mouse strain (CA3-*NR1*-knockout mice) in which the *NR1* gene deletion was restricted to the CA3 pyramidal cells of adult mice[68]. These mutant mice were impaired in the DMP version of the MWM task that was conducted with a 5-min intertrial interval. By contrast, mutant mice performed normally when previously experienced platform locations were used and in the standard version of the MWM. These results showed that CA3 NMDARs are crucial for the rapid acquisition of one-trial memory of novel spatial information[69]. Spatial tuning of CA1 place cells in mutant mice was normal in a familiar environment but was significantly impaired (with enlarged place fields and an augmented integrated firing rate) in a novel environment[69]. Strikingly, when the mutants were re-exposed to the 'novel' environment after being held in a home cage for 1 day, spatial tuning was normal. So, the tuning deficit is seen only during a defined period (at least 1 hour) after exposure to a novel environment, and some consolidation process occurs in the absence of the continuous environmental information, resulting in normal tuning by the next day.

It has been suggested that entorhinal neurons provide an important input to CA1, particularly during tasks that require the encoding of novel information[70–72]. FIGURE 3 shows a model for the role of NMDARs in CA3 in the rapid establishment of highly tuned CA1 place cells when animals are exposed to novel spatial information. During exposure to a novel context, the CA1 response is initially and transiently driven by direct input from the EC, which is spatially broadly tuned[73–75]. In control animals, NMDAR activity in CA3, perhaps operating through Hebbian recurrent connections, allows the rapid formation of CA1 place cells as the input from CA3 comes to dominate and shape the EC input. This shift of dominant input from EC to CA3 occurs so rapidly that it is difficult to observe the initial, less tuned state of CA1 place cells. By contrast, in CA3-*NR1*-knockout mice, as a consequence of CA3 NMDAR ablation, the less spatially-tuned EC place cells continue to drive CA1 place-cell activity for at least one hour after exposure to a novel space. Subsequently, however, by the time the mutants are re-exposed to the same context 1 day later, a slow spatial refinement of CA1 place fields seems to have been implemented off-line. It is not known which hippocampal circuitries and synapses are involved in this slow refinement process. However, knife cuts of the connections between CA3 and CA1 do not block reactivation of CA1 place cells on re-exposure to a familiar environment[72]. This suggests that the temporoammonic pathway and its synaptic plasticity might be sufficient for this process[76]. Although CA3 NMDARs seem to be crucial for the rapid formation of highly tuned CA1 place cells, their ablation does not seem to block encoding of the novel information entirely. If it did, it would be difficult to explain the presence of highly tuned place cells on re-exposure on day 2 (REF. 69).

Overall, the combined behavioural and physiological analyses of the CA3-*NR1*-knockout mice and the behavioural analysis of AP5-treated rats indicate that CA3 NMDARs are crucial for rapid hippocampal encoding of novel information, which is necessary for rapid learning of one-time experience. A recent study on a new PAIRED-ASSOCIATE TASK is consistent with this conclusion, reporting that the encoding of a 'what–where' association between a specific odour and a location depends on hippocampal NMDARs[77].

PAIRED-ASSOCIATE TASK
A task that involves the arbitrary association of two stimuli (such as word pairs in humans, or a place and an odour or food item in animals). After exposure to the pair, the subject is presented with one stimulus and tested for recall of the second. It can be used to test declarative memory in humans, or 'episodic-like' memory in animals.

Memory consolidation

It is commonly thought that input from the external world is initially encoded as nascent neural firing patterns and is later stored in a more persistent form. Ebbinghaus[78] first mentioned this phenomenon as the 'overlearning effect', and Müller and Pilzecker[79] proposed this as a 'consolidation theory', an idea later refined by Hebb[10]. Memory is labile for a short time after its acquisition, and treatments such as protein synthesis inhibition, electro-convulsive shock or hypothermia can lead to memory loss[80–82]. Two main mechanisms have been proposed for 'memory consolidation'. One, 'trace-transfer consolidation', emphasizes the transfer of a memory trace over time, for instance, from the hippocampus to the cortex[1]. This between-structure transfer is sometimes referred to as 'systems consolidation'[65,66,83–86]. The second — cellular consolidation — focuses more on the molecular events in cells in a given brain region. It has been suggested that the initially fragile memory trace is made more permanent through biochemical and morphological synaptic and cellular changes that mark the transition from short-term to long-term forms of plasticity[87–90]. System consolidation and cellular consolidation are not mutually exclusive. Rather, it is likely that cellular consolidation occurs in both pre-transfer (for example, hippocampus) and post-transfer (for example, neocortex) brain systems[82].

Briefly, cellular consolidation is initiated by the activation of NMDA, AMPA and metabotropic glutamate receptors, and involves changes in the levels of second messengers, followed by enhanced activity of protein kinases such as PKA, PKC, PKG and the calmodulin (CaM) kinases, as well as protein phosphatases such as PP1, PP2A and PP2B. These molecular events lead to *de novo* transcription through the activation of constitutive and inducible transcriptional factors such as the cyclic-AMP-responsive element-binding (CREB) family of proteins[91–100]. Additional regulation can also occur at the level of mRNA transport and translation[101–103].

Post-training infusion of NMDAR antagonist. To examine the role of NMDARs in memory consolidation, Morris *et al.* infused AP5 into the ventricles of rats that had been trained on the hidden-platform MWM task. A dose that impaired learning when administered before training had no effect when administered 1 day after training[32,36]. These data support the notion that NMDARs are needed for memory acquisition but not for consolidation. Further support for this idea came from experiments in which AP5 and MK801 were administered intra-ventricularly and systemically, respectively, 4 days after the last training day without effect[104], and from a study in which post-training administration of MK801 had no effect on a probe trial 24 h later[105]. On the other hand, Packard and Teather[106,107] reported that injection of AP5 or MK801 into rat hippocampus immediately after training on the MWM task impaired the rats' memory when they were tested 24 h later. These authors defined the NMDAR-dependent time window to be less than 2 h after completion of the training; however they used an unusual training protocol that consisted of a single session composed of eight continuous trials.

In all of these studies, both the demands of the task and the drug administration methods varied greatly and it is not easy to compare the results and produce a coherent interpretation.

In studies that seemed to show a function for NMDARs in memory consolidation, no attempt was made to restrict NMDAR blockade to a particular brain system. Therefore, it is impossible to decide whether the effects were exerted in the neocortex or hippocampus. Shimizu *et al.*[108] attempted to address this issue by combining the tTA (tetracycline-dependent transactivator protein)[109] and Cre/*loxP* techniques to develop a mouse line in which NMDAR ablation was both regionally and temporally controlled. Treatment with doxycycline 1–7 days after training caused inhibition of NR1 expression in hippocampal CA1 pyramidal cells and an impairment in memory. Delaying NR1 inhibition to 9–14 days after training prevented the memory impairment. The authors concluded that the reactivation of NMDARs in the hippocampus (that is, in CA1) is necessary for cellular consolidation[108]. However, the restriction of NMDAR inhibition to CA1 in this mouse strain was not clearly demonstrated in their study. A recent analysis of the CA1-*NR1*-knockout mice that were used in this study showed that the absence of the NR1 subunit spread to the neocortex after 2 months of age[42], so it is premature to conclude that reactivation of hippocampal NMDARs is needed during memory consolidation.

Some studies have hinted at the involvement of NMDARs in cellular memory consolidation, but further investigation is needed to establish the role of hippocampal NMDAR function in consolidation. It should also be noted that the hidden-platform MWM is not an ideal paradigm for dissociating acquisition and consolidation, because multiple training trials lasting several days will inevitably make the two phases overlap. A paradigm such as contextual fear conditioning, in which one to a few training trials are sufficient for acquisition, would be a method of choice.

Memory retrieval

In the aforementioned studies on the role of NMDARs in cellular consolidation, the effect of an intervention treatment on consolidation as opposed to retrieval was distinguished by the duration between the time of the completion of the training session and the time of the treatment. This requires us to assume that a memory test conducted soon after the completion of training measures consolidation and/or retrieval, but a test conducted long after training tests only retrieval. Based on this assumption, there is accumulating evidence that the ablation of hippocampal NMDAR function has little effect on memory retrieval. Early evidence for this came from a hippocampus-dependent olfactory discrimination task[110] and a spatial reference memory task[32,36]. Later, as mentioned above, similar results were obtained by pharmacological[106] and genetic intervention[108]. Other behavioural tasks have also shown a role for hippocampal NMDARs in encoding but not in retrieval. These include inhibitory avoidance[111–114] with the memory tests conducted immediately after or 24 h after the end of training.
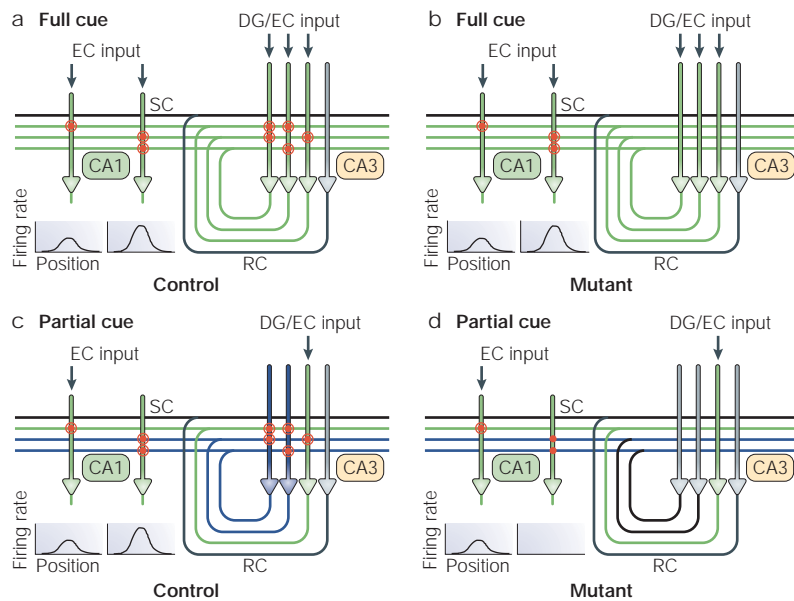
Figure 4 | Spatial pattern completion model in hippocampal networks. In control animals, during memory acquisition under full-cue conditions, both recurrent collateral (RC) synapses within CA3 and Schaffer collateral (SC) synapses in CA1 are modified in an NMDAR (*N*-methyl-D-aspartate receptor)-dependent manner, leading to storage of the memory trace (small red dots) in CA3 and CA1, respectively (**a** and **c**). In CA3-*NR1*-knockout mice this will happen in CA1 but not in CA3 (**b** and **d**). During the recall phase, if the full set of cues is presented, CA1 memory traces will be fully activated in both control and mutant animals, leading to full recall (**a** and **b**). If only a partial set of cues is provided to control animals, it will initially activate only partial CA3 memory traces, but because of the robust connections among CA3 cells, activation of the entire CA3 memory traces will be accomplished subsequently by iteration of activity within the recurrent CA3 network. This will, in turn, activate the entire CA1 memory trace (**c**). In mutants, because of the lack of memory traces in the recurrent CA3 network, which prevents iteration-mediated trace activation, CA1 memory traces will not be fully activated (**d**). So, mutants exhibit impaired recall under partial-cue conditions. Vertical arrows designate inputs from recall cues. Red dots with circles indicate reactivated memory trace components[68]. DG, dentate gyrus; EC, entorhinal cortex. Modified, with permission, from REF. 68 © (2002) American Association for the Advancement of Science.

A likely reason for the dispensability of NMDARs in retrieval comes from evidence that blockade of hippocampal CA1 NMDARs has little effect on AMPAR-mediated fast synaptic transmission[11]. So, even if NMDAR blockade could completely freeze the existing pattern of synaptic weights in the hippocampus, the cells would be able to fire and to faithfully transmit the established network pattern using AMPA/kainate receptors[115,116].

CA3 NMDARs for associative memory recall. Marr suggested that the recall process could occur either in one step — 'simple recall' — or in a series of steps involving recurrent network activation — a 'collateral effect'[28]. Personal experiences in daily life are unique and rarely repeat exactly[28,117]. So, input patterns that change from moment to moment would be able to reactivate only part of a stored memory and would be unable to activate the whole pattern without repeated iterations of firing in the recurrent network. This concept is called 'pattern completion'[28]. The presence of massive recurrent collaterals with highly modifiable synapses made area CA3 an attractive candidate site for the biological implementation of this process, which is required for the retrieval of hippocampus-dependent associative memory[26,118–122].

In the hidden-platform MWM task, the training (memory acquisition) and probe (memory retrieval) trials are usually carried out in the same environment[16,40]. Although this protocol provided basic insights into the mechanisms of memory formation, it is not optimal for investigating the mechanism that underlies memory recall by pattern completion. Nakazawa *et al.* trained CA3-*NR1*-knockout mice in the hidden-platform MWM task under full-cue conditions and then subjected them to probe trials either under the same full-cue conditions or under conditions in which some of the cues were removed (degraded-cue conditions)[68]. Although the mutant mice acquired the spatial reference memory and retrieved it normally under the full-cue conditions, they were impaired at retrieving the memory under degraded-cue conditions, unlike control mice. These data indicated that CA3 NMDARs, in contrast to CA1 NMDARs[41], were not necessary for the acquisition of spatial reference memory that could be retrieved under full-cue conditions, but that CA3 NMDARs were important for recalling the spatial reference memory when only a fraction of the cues were available. Recordings from place cells in area CA1, downstream of CA3, corroborated these behavioural data; when CA3-*NR1*-knockout mice were allowed to explore a full-cue environment repeatedly, place cells with normal spatial tuning properties were formed and they were fully reactivated when the animals were returned to the environment after several hours in a home cage. By contrast, when the mutants were returned to an environment in which only a fraction of the original cues were available, the place-cell reactivation was severely impaired. These behavioural and physiological data, along with the finding that CA1-*NR1*-knockout mice showed a severe deficit in the acquisition of the hidden-platform MWM task[40] and uncoordinated, spatially less-tuned CA1 place-cell activity[41], led Nakazawa *et al.* to conclude that CA1 NMDARs are essential for the acquisition of spatial reference memory but that CA3 NMDARs are not. Instead, CA3 NMDARs are crucial for the retrieval of the memory under conditions in which pattern completion is required. According to this proposal, the primary deficit in CA3-*NR1*-knockout mice was in the formation of NMDAR-dependent ensemble memory traces in CA3. This manifested as a deficit in recall by pattern completion (FIG. 4).

NMDAR function and place cells
Since O'Keefe and Nadel[123] first proposed that the hippocampus is a neural substrate of a 'cognitive map' and described the mnemonic aspects of place-cell activity, tremendous effort has been made to determine whether place-cell activity is directly related to the formation and expression of spatial memory traces. BOX 3 lists the conditions that must be met by any physiological process to be called a memory trace. Many studies have provided evidence that the pattern of place-cell activities can be viewed as an expression of a memory trace at the neuronal ensemble level[123–130]. Most convincingly, place cells show spatially characteristic stable firing patterns across temporally separated recording sessions — a

unique set of place cells is reactivated on subsequent exposure to the same environment, and these patterns can be subsequently reactivated independently of behaviour[124,127,128,131–133]. In addition, the entire set of place cells can be reactivated by a subset of the original set of cues[68,134–137]. These features of place cells satisfy criteria 2, 3 and 4 in BOX 3. However, it has been difficult to show directly that place-cell formation is experience dependent (criterion 1). It has been shown that in a novel space the ensemble code, which is initially less robust, improves rapidly with exploration; however, this change is so rapid that improvements in the coding of individual cells have been impossible to monitor[125]. Although Mehta *et al.* have reported lap-dependent modifications of preexisting place fields[138,139], the initial changes in place-field size that might represent the acquisition of novel spatial information have not been fully characterized. The ablation of NR1 in area CA3 slows down the *de novo* formation of CA1 place fields[69]. Although the kinetics and mechanisms of the maturation of these place fields have not been fully characterized, the enlarged place fields that were observed during the first hour of exposure became condensed to normal sizes in the home cage before reexposure to the same environment the next day. If these enlarged place fields represent an early, transient state of place-cell formation, this finding supports the experience dependency of place-cell formation, and therefore the role of these cells in a memory trace.

Other groups have used pharmacology to address the role of the NMDAR in the hippocampal encoding of space. Kentros *et al.* examined the differential effects of systemic administration of the NMDAR antagonist CPP (3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid) on the formation and maintenance of CA1 place cells[140]. The global blockade of NMDARs had no effect on the formation and short-term stability of CA1 place cells in a novel environment, nor on the reactivation of place cells in a familiar environment. The observation of normal place fields in novel space in the absence of NMDAR function seems to contradict the finding of enlarged and diffuse CA1 place fields in CA3-*NR1*-knockout mice[69].

Ekstrom *et al.*[141] used pharmacological blockade to test whether NMDAR-mediated plasticity is necessary for the experience-dependent asymmetric shift of established CA1 place fields[139]. Treatment with CPP caused a deficit in the lap-dependent skewing of fields and, as a result, slightly smaller fields. This reduction of place-field sizes also contradicts the enlarged and diffuse CA1 fields of

CA1-*NR1*-knockout mice in familiar environments[41]. One possible explanation for the differences in the spatial tuning properties of place cells in pharmacologically treated and genetically engineered rodents is that the genetic interventions (even if they occur only postnatally) are not as acute as the pharmacological ones. So, the NR1 deletion might have led to an accumulation of cellular and/or system level changes, and these might have contributed to the phenotype. Conversely, the genetic lesion was more targeted and more complete, so it might have revealed more specific deficits. For instance, the establishment of place fields could require a balance of excitation and inhibition on both the cellular and circuit levels. Systemic administration of CPP is expected to inhibit NMDARs on both excitatory and inhibitory cells involved in place-field formation, possibly in a coordinated fashion, leading to the apparently normal phenotype. By contrast, the genetic NR1 blockade was restricted to the excitatory neurons, and so might have led to the impairment. The future application of cell-type-specific, rapidly inducible genetic manipulation could address these issues and clarify the matter.

Although the study of Kentros *et al.*[140] lacks regional specificity, it does have the advantage of precise temporal control and therefore has shed light on the relationship between NMDARs and the stability of CA1 place fields. Place fields that formed *de novo* in the presence of CPP were unstable, but CPP had no effect on the maintenance of previously established place fields[140]. These results are consistent with behavioural evidence that hippocampal NMDARs are required for the acquisition and perhaps the initial consolidation of hippocampus-dependent memory, but not for its maintenance. Other studies with transgenic mice in which signalling and transcriptional molecules downstream of the NMDAR were altered also showed similar effects on the stability of place fields[142–145]. However, one should apply caution in interpreting these data because it is technically difficult to maintain stability in the electrophysiological isolation and identification of cells recorded across days in these long-term recording experiments.

Conclusions

We have summarized recent advances in our understanding of the roles of NMDARs in the acquisition, consolidation and recall of hippocampus-dependent memory with a focus on spatial memory. Behavioural studies of rodents in which NMDAR function is blocked by pharmacological or genetic manipulations indicate that hippocampal NMDARs are crucial for the acquisition of hippocampus-dependent memory, and particularly for 'episodic-like' memory. Whether hippocampal NMDARs are involved in the cellular consolidation of memory remains to be determined, but they do not seem to be directly involved in memory retrieval. Cell-type-restricted gene ablation techniques are beginning to reveal distinct mnemonic functions of NMDARs in the different hippocampal areas and circuits. So, although NMDARs in CA1 pyramidal cells seem to be crucial for the acquisition of spatial reference memory, NMDARs in CA3 pyramidal cells are not.

Instead, CA3 NMDARs seem to be important for the rapid acquisition of one-trial memory (episodic-like memory) and for the retrieval of associative memory by pattern completion.

Although these behavioural studies with pharmacologically or genetically engineered rodents have contributed greatly to our understanding of the importance of NMDAR-dependent synaptic plasticity in hippocampus-dependent memory, it is unlikely that a memory trace resides at an individual synapse with modified transmission efficacy. As Hebb proposed, memory is likely to be encoded in the pattern of activity of a cellular ensemble, the individual components of which are connected by synapses with modified synaptic efficacy[10]. In several studies in which the *NR1* gene knockout was targeted to hippocampal CA1 or CA3 pyramidal cells of adult mice, the spatial tuning qualities of CA1 place cells were determined under conditions that mimicked those under which behavioural aspects of hippocampal-dependent learning and memory were examined. The deficits in the spatial tuning quality of place cells, both at the individual and ensemble cell levels, correlated well with the impairments of behaviourally assessed learning and memory. In addition, the analyses of the abilities of CA3-*NR1*-knockout mice in rapid one-trial learning and in the encoding of a novel

space led to evidence for experience-dependency of place-cell formation, an important attribute of an ensemble memory trace. The effects of NMDAR antagonists on the long-term stability of CA1 place cells correlated well with the effects of these agents on the acquisition and consolidation of spatial memory. All of these studies support the idea that hippocampal place cells are an excellent candidate for an ensemble memory trace. However, most of the evidence that led to this notion concerns spatial encoding and spatial memory and in almost all of these studies, the recording of place cells have been carried out, for technical reasons, in setups that mimic, but are not identical to, those of the learning and memory tasks. So, one challenge for future studies is to devise a paradigm with which memory and place-cell activities can be assessed simultaneously. There is also still much to be learned about how information relating to non-spatial parameters, such as behavioural state, motivation and olfactory and other sensory inputs, is encoded by and represented in place-cell activity[146–151].

With further multidisciplinary studies consisting of conditional transgenic technology, *in vivo* multi-unit recording and clever behavioural paradigms, we might move closer to our ultimate goal of understanding the molecular, cellular and neuronal ensemble mechanisms for hippocampus-dependent learning and memory.

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Nakazawa's homepage: http://neuroscience.nih.gov/Lab.asp?Org_ID=496
Tonegawa's homepage: http://www.hhmi.org/research/investigators/tonegawa.html
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