OPINION

Hippocampal synaptic plasticity, spatial memory and anxiety

David M. Bannerman, Rolf Sprengel, David J. Sanderson, Stephen B. McHugh, J. Nicholas P. Rawlins, Hannah Monyer and Peter H. Seeburg

Abstract | Recent studies using transgenic mice lacking NMDA receptors in the hippocampus challenge the long-standing hypothesis that hippocampal long-term potentiation-like mechanisms underlie the encoding and storage of associative long-term spatial memories. However, it may not be the synaptic plasticity-dependent memory hypothesis that is wrong; instead, it may be the role of the hippocampus that needs to be re-examined. We present an account of hippocampal function that explains its role in both memory and anxiety.

The ability to learn and remember spatial locations, and to associate them with other stimuli, is an essential adaptive behaviour that is required for survival. Spatial navigation and spatial memory are primarily associated with the hippocampus, both in rodents and humans[1,2]. Much of the evidence for this has come from lesion studies using spatial memory tasks (particularly in rodents[3–6] (BOX 1)), the observation of place cells in rodents[7] and, more recently, from functional MRI (fMRI) studies in humans[8,9]. However, these approaches are limited, as they typically provide little information about the psychological, synaptic and molecular mechanisms that underlie spatial information processing.

By contrast, studies using genetically altered mice in which NMDA receptors (NMDARs) and AMPA receptors (AMPARs) have been selectively manipulated show striking dissociations within spatial memory, revealing important information about the psychological processes that underlie performance on different spatial memory tasks. For example, studies of mice lacking the gene encoding the GluA1 subunit of the AMPAR (*Gria1*$^{-/-}$ mice) have revealed clear dissociations between spatial working memory (SWM) and spatial reference memory (SRM) (FIG. 1), which indicate that spatial memory is not a single process but instead has distinct forms (BOX 2). These dissociations, which had remained undetected despite decades of lesion studies, can now be understood in terms of distinct psychological processes underlying short- and long-term spatial memory[10,11]. Moreover, recent studies using hippocampus-specific NMDAR-knockout mice have even revealed dissociations between performances on different SRM tasks (such as water maze and radial maze tasks) (BOX 1), which challenge long-standing views about the importance of hippocampal synaptic plasticity, particularly long-term potentiation (LTP), for the encoding and storage of associative long-term spatial memories. In this article, we argue that hippocampal LTP is not required for encoding associative long-term spatial memories (although synaptic plasticity outside the hippocampus may be necessary) and, given these more recent data, that the precise role that the hippocampus has in memory processing needs to be reconsidered.

What is spatial memory?

What constitutes a spatial cue or makes a behavioural task spatial in nature? Spatial cues are generally considered to be complex multimodal representations of the environment that comprise information from different sensory modalities. Some spatial tasks can be performed using 'egocentric' (self-centred) information (for example, using vestibular or proprioceptive cues), but other spatial tasks require encoding of the relationship between salient features of the environment to create an 'allocentric' (other-centred) spatial representation that is independent of the animal's current location. For example, it is important for an animal to be able to find its way home from new starting positions (for example, if it is forced to leave a customary route and find a new way home).

O'Keefe and Nadel[1] proposed that there are two distinct systems that guide spatial learning and memory. The first of these, the 'taxon' system, uses egocentric cues and specific behavioural responses to specific landmarks or stimuli to enable route-based navigation (for example, always turn right, always approach stimulus X, always move away from stimulus Y, and so on). The second system, the 'locale' system, underlies allocentric spatial encoding and the formation of a cognitive map of the environment. The locale system becomes important when it is not possible to rely on always approaching stimulus X or always moving away from stimulus Y. O'Keefe and Nadel[1] hypothesized that this cognitive map is maintained in the hippocampus, with place cells as its basic functional units. It was found that cells in the hippocampus of behaving rats selectively increased their firing rate only when the rat occupied a well-defined region of the environment, the 'place field', and rarely fired outside the place field[7]. Logically, these cells were named 'place cells'. More recently, glutamatergic cells with different firing properties have been identified in the hippocampal formation, including grid cells in the entorhinal cortex[12,13], head direction cells in the subiculum[14,15] and boundary vector cells in both of these regions[16–18].

Consistent with this hypothesis, hippocampal lesions in rodents impair allocentric but not egocentric spatial memory[4,5,19] across a wide range of tasks, including the Morris water maze[4,5], the radial maze[3,20], T-maze-rewarded alternation[6] and many others (BOX 1). Indeed, the hippocampus plays an important part in allocentric spatial information processing in a great many species, including humans[2,8,9].

Box 1 | **Behavioural tests of long-term spatial memory in rodents**

Allocentric spatial learning and memory is assessed in rodents using a wide range of tasks, and performance on all of these tasks is impaired by hippocampal lesions. Owing to the large number and variety of tasks used, a detailed description of all of these paradigms is beyond the scope of this article. Below are descriptions of the two key tasks that are most widely used to assess associative long-term spatial reference memory (SRM) in rodents.

Open-field water maze

In this task, rodents have to locate a hidden escape platform that is submerged just beneath the surface of the water in a large circular tank. In the standard SRM version of the task, the animal is trained to remember the same fixed platform location over several days. Although the platform remains in the same position throughout training, crucially, the starting position changes on each trial to prevent the use of egocentric strategies (for example, body-turn) to find the platform. Latencies and path lengths to locate the platform are recorded. In addition, spatial memory can be measured with transfer (probe) tests during which the platform is removed from the pool and the animal is allowed to swim freely for 60 seconds. Animals with good spatial knowledge of the platform location will spend most of the time searching in the appropriate region of the pool (the target quadrant).

Radial arm maze

SRM and spatial working memory (SWM) can be assessed in the same animals using the radial arm maze. The radial maze consists of a number of arms (commonly 6, 8 or 12) radiating out from a central area like spokes on a wheel. The aim of the task for the animal is to collect hidden food rewards located at the ends of the arms by using the distal extramaze cues around the laboratory. SRM can be assessed by rewarding only certain arms but always rewarding the same arms. If an animal enters a non-rewarded arm then an error is scored. During SRM acquisition, animals are prevented from making any SWM errors by closing off the access to an arm after it has been visited[20]. Thus, animals can only enter each arm once during this first phase. In the second phase of the experiment, SRM and SWM are simultaneously assessed. Mice are now no longer prevented from re-entering an arm, but the food rewards are not replaced within a trial. Because the food rewards are not replaced between choices within a single visit to the maze, the animal has to adopt a win–shift strategy (that is, when it 'wins' a reward it then has to 'shift' to a different choice to gain further reward) and thus remember which arms it has already visited. This provides a test of SWM.

Synaptic plasticity and spatial memory

It is essential to be able to associate particular spatial locations, within an environment or a cognitive map, with particular events or outcomes, such as reward or danger. It had been widely suggested that associative memories are stored as changes in the strength of the synaptic connections between neurons[21–23]. The subsequent discovery that high-frequency stimulation of an input pathway can produce long-lasting changes in synaptic efficacy[24] led to LTP becoming the dominant experimental model of the cellular mechanisms of learning[25]. In particular, the idea that LTP (or an LTP-like mechanism) in the hippocampus supports associative spatial memory formation (that is, associating particular spatial locations within a cognitive map with particular events, outcomes or stimuli) has been widely accepted[26] and has only rarely been questioned[27–32]. However, recent evidence from a novel genetically modified mouse line challenges the relationship between hippocampal LTP and associative long-term spatial memory formation[33].

The role of hippocampal NMDARs in SRM tasks. The induction of the most commonly studied form of LTP depends on the activation of NMDARs[34]. It has become widely accepted that NMDAR signalling and NMDAR-dependent synaptic plasticity in the hippocampus are essential for encoding associations between particular events or outcomes and specific spatial locations within a cognitive map[26].

In order to test this hypothesis and establish a causal link between hippocampal LTP and spatial learning abilities, it is necessary to show that preventing the induction of LTP in the hippocampus impairs spatial learning. To this end, two main approaches have been adopted. First, a pharmacological approach was used to assess the effects of NMDAR antagonists (such as AP5), which block the induction of LTP, on spatial learning and memory. Second, genetically modified mice lacking NMDARs in specific brain regions and neuronal cell types were also used to test the hypothesis. With the advantage of hindsight, it is now clear that many of these studies incorporate weaknesses of methodology or interpretation that limit the conclusions that can be drawn from their data. We first briefly review these older studies and then describe data from a novel genetically modified mouse line, from which stronger conclusions can be drawn.

NMDAR antagonists and spatial learning. Morris and colleagues[35–37] showed that blocking NMDARs by intracerebroventricular (ICV) infusion of the specific antagonist AP5 impaired acquisition of the SRM water maze task at concentrations that also blocked LTP in the dentate gyrus *in vivo*. However, given the ICV route of drug administration, there followed considerable debate as to the brain locus of these effects (hippocampal (CA and dentate gyrus subfields) versus extra-hippocampal) and whether the deficit in performance of these animals in the water maze reflected a learning impairment or a non-specific disruption of sensorimotor or motivational aspects of task performance[27,30,31]. Furthermore, subsequent pharmacological experiments showed that AP5-treated rats could in fact solve the SRM water maze task if they had received water maze pre-training in a different spatial environment before testing with the drug (the spatial upstairs–downstairs task)[32,38]. This result suggested that hippocampal NMDARs were not after all essential for forming a spatial representation of a novel environment, for forming an association between a particular spatial location and the escape platform or for efficient spatial navigation through an environment.

Studies with NMDAR subunit-knockout mice. Advances in genetic engineering provided an alternative approach for testing the LTP-dependent memory hypothesis. Genetic engineering enabled the ablation of key proteins that are required for either the induction or expression of LTP, such as NMDAR subunits, and the effects on behaviour were then studied. The NMDAR is a tetrameric membrane-inserted protein complex, comprising two obligatory GluN1 subunits (which are essential for forming NMDARs) and two GluN2 subunits[39,40]. The major GluN2 subunits in the adult neocortex and hippocampus are GluN2A (formerly known as the NR2A or the ε1 subunit) and GluN2B.

The first study on an NMDAR-knockout mouse initially seemed to be consistent with the LTP-dependent memory hypothesis. This study reported that mice lacking the gene encoding the GluN2A subunit of the NMDAR throughout the brain (*Grin2a*$^{-/-}$ mice) showed impairments in

performance on the standard water maze task and also showed reduced hippocampal LTP[41]. However, in marked contrast to this original report, subsequent studies carried out after extensive backcrossing to the C57BL/6 strain[42] found that *Grin2a*$^{-/-}$ mice actually performed as well as their wild-type littermates on the standard SRM version of the water maze task[43]. Mice in which the carboxy-terminal intracellular domain of the GluN2A subunit was selectively deleted (*Grin2a*$^{\Delta C/\Delta C}$ mice) also showed normal SRM. Notably, both the *Grin2a*$^{-/-}$ and *Grin2a*$^{\Delta C/\Delta C}$ mice showed impairments in SWM tasks, and in a spatial novelty preference task, which suggests that the GluN2A subunit has an important role in non-associative short-term memory processes (BOX 2).

Hippocampus-specific GluN1-knockout mice. A crucial advance in validating the hippocampal LTP-dependent spatial memory hypothesis seemed to have arrived with the generation of region-specific conditional knockout mice. Mice in which *Grin1*, the gene encoding the obligatory GluN1 subunit of the NMDAR, was reported to be selectively ablated from the dorsal CA1 subfield of the hippocampus were made using the transgenic Cre recombinase-expressing line *Tg-29-1* (REFS 44,45). The impairment in SRM in the water maze task described in these conditional *Grin1*-knockout mice and the absence of LTP at Schaffer collateral–CA1 synapses were taken as confirmation that associative long-term spatial memories are indeed encoded in the hippocampal CA1 region through an NMDAR-dependent LTP-like mechanism[45]. In fact, this result rapidly became the cornerstone of the hippocampal LTP-dependent spatial memory hypothesis.

However, this study has also failed to stand up to subsequent scrutiny. The genetic manipulation was less selective than initially believed. Subsequent studies in these conditional *Tg-29-1 Grin1*-knockout mice demonstrated that the NMDAR depletion extended beyond the hippocampus and spread into cortical areas, thus confounding interpretation of the SRM impairment in the water maze task[46–50]. More recent publications have reported a clear reduction in cortical GluN1 expression in these animals as early as 2 months of age[48,50], if not sooner, and other studies have demonstrated Cre expression in the cortex of the *Tg-29-1* line as early as 6 weeks after birth[46]. Consistent with extra-hippocampal NMDAR ablation, the performance of conditional *Tg-29-1 Grin1*-knockout mice is also significantly impaired on a non-spatial version of the water maze task. Therefore, it is not possible to attribute the spatial memory deficit in the water maze task in these mice specifically to NMDAR loss in the hippocampus.

A dissociation in long-term SRM. Recent generation of a novel genetically modified mouse line has provided an alternative way to test the hippocampal LTP-dependent spatial memory hypothesis. In this line, the GluN1 subunit is selectively deleted from dentate gyrus granule cells and dorsal CA1 pyramidal cells of adult mice (*Grin1*$^{\Delta DGCA1}$ mice[33]), leaving NMDARs in the cortex and elsewhere in the brain intact (FIG. 2a). The loss of NMDARs from CA1 and dentate gyrus principal cells results in the loss of LTP at CA3–CA1 synapses in these mice and, surprisingly, a reduction in the number of granule cells in the dentate gyrus. Nevertheless, these *Grin1*$^{\Delta DGCA1}$ mice perform perfectly well on the SRM version of the Morris water maze task (FIG. 2b). In fact, on probe tests in which the platform is removed from the pool and the mice are allowed to swim freely for 60 seconds, *Grin1*$^{\Delta DGCA1}$ mice actually spend more time searching in the target quadrant than control mice.

By marked contrast, the performance of *Grin1*$^{\Delta DGCA1}$ mice is impaired on the SRM version of the radial maze task in which they have to learn to discriminate between always-rewarded and never-rewarded arms (BOX 1; FIG. 2c). Notably, mice in which the GluN1 subunit is selectively deleted just from dentate gyrus granule cells do not exhibit impaired performance on the SRM radial maze task[51], demonstrating that NMDARs in the CA1 subfield make an important contribution to performance on this task (BOX 3).

This dissociation between the two classic tests of associative long-term SRM clearly indicates that different psychological processes must be involved in the two tasks. These psychological processes were identified by a further water maze experiment. *Grin1*$^{\Delta DGCA1}$ mice were trained on a spatial discrimination task in which two visually identical beacons were located just above the water surface, only one of which indicated the position of the hidden escape platform (FIG. 3a). The correct and decoy beacons were differentiated solely by their allocentric spatial locations relative to the extramaze room cues. Although *Grin1*$^{\Delta DGCA1}$ mice were again capable of learning the spatial location of the platform (as measured using probe tests,

Glossary

AP5
(2-amino-5-phosphopentanoate). A competitive antagonist of the NMDA-type glutamate receptor. The drug competes with glutamate to bind to the NMDA receptor and thus reduces the activity of these receptors.

Boundary vector cells
The firing of these cells depends solely on the animal's location relative to environmental boundaries and is independent of the animal's heading direction.

Dissociations
A term to describe when an experimental manipulation (for example, a lesion, genetic modification or drug treatment) affects performance on one behavioural task but not another. This is taken to suggest that different neural substrates may underlie the two behaviours.

Double dissociation
A term to describe when a given experimental manipulation affects task A but not task B, whereas a second manipulation affects task B but does not affect task A. A double dissociation is evidence that these behaviours must be supported by different neural substrates.

Grid cells
Cells that have been found in layer 2/3 of the medial entorhinal cortex and that fire at several regularly spaced locations (unlike hippocampal place cells, which fire only in one part of a given environment), with marked inhibition of firing outside these locations.

Head direction cells
Cells that are sensitive to the orientation of the animal's head with respect to the environmental frame, irrespective of the animal's spatial location within that environment. They signal a single preferred head direction, irrespective of body-orientation or current position; whether the animal is moving or stationary.

Place cells
Cells that selectively increase their firing rate only when the animal occupies a well-defined, small patch of the environment (the place field), and they rarely fire outside this region. Place cells are usually recorded in the hippocampus proper, but they are also present in other areas of the hippocampal formation (for example, the entorhinal cortex, subiculum, presubiculum and parasubiculum).

Spatial reference memory
(SRM).The ability to learn a consistent, fixed response to a spatial stimulus, reflecting a constant association between that spatial location and an outcome. For example, an animal will need to learn the spatial location of its home burrow or a reliable water source that is constant within the environment.

Spatial working memory
(SWM). The ability to maintain trial-specific information for a limited period of time so that spatial responses can be made in a flexible manner from trial to trial. This is the basis of foraging behaviour (for example, remembering where you have just been so that you can adopt an efficient search strategy).

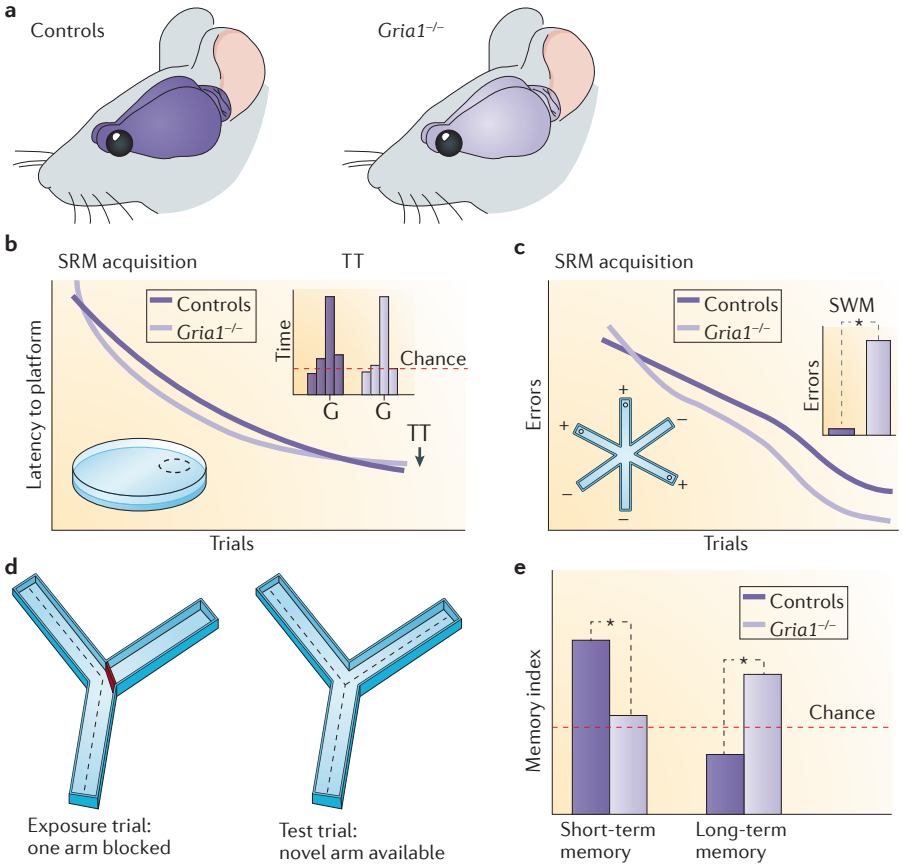

Figure 1 | **GluA1 is required for short-term, but not long-term spatial memory.** **a** | Mice lacking the gene encoding the GluA1 AMPA receptor subunit (*Gria1*$^{-/-}$ mice) and wild-type control mice were compared on tests of spatial memory. **b** | GluA1 is not required for spatial reference memory (SRM) in the water maze task[129,130]. *Gria1*$^{-/-}$ mice and control mice exhibited similar latencies to find a hidden escape platform in a fixed spatial location (shown as a dashed circle) during acquisition training. They also showed an equivalent preference for the goal (G) or target quadrant (that is, the quadrant that normally contains the platform) during a transfer (probe) test (TT) conducted at the end of acquisition training, during which the platform was removed from the pool and the mice were allowed to swim freely for 60 seconds (see inset, where each bar on the histogram represents the time spent in a quadrant of the pool). **c** | GluA1 is required for spatial working memory (SWM), which depends on short-term memory, but not for SRM, which depends on long-term memory, in the radial maze. Mice were trained to discriminate between arms of the radial maze that contained a food reward (+ arms) and arms that were never rewarded (– arms); entry into a never-rewarded arm constituted an SRM error. Note that mice were prevented from making SWM errors during the SRM acquisition phase. *Gria1*$^{-/-}$ mice exhibited faster acquisition of the SRM component of the radial maze task than wild-type control mice, making fewer SRM errors as training proceeded[20]. By contrast, in a subsequent test of SWM, *Gria1*$^{-/-}$ mice repeatedly re-entered arms that they had already visited on that trial and that were no longer rewarded (therefore making SWM errors). *Gria1*$^{-/-}$ mice made more SWM errors than wild-type mice[20,140] (see inset; the asterisk indicates a statistically significant difference). **d** | The absence of short-term spatial memory in *Gria1*$^{-/-}$ mice can result in the facilitation of long-term spatial memory in these animals. *Gria1*$^{-/-}$ mice showed impaired short-term spatial memory, but by contrast they actually demonstrated enhanced long-term spatial memory, which can be measured using a simple, novelty preference test in an enclosed Perspex Y-maze, surrounded by distal extramaze cues. During multiple 'exposure trials', mice are allowed to explore two arms of the Y-maze (one arm is blocked off). Then during the 'test trial', the mice are free to explore all three arms of the maze (the novel, previously unvisited arm is now available), and the time spent in each arm is recorded. Short and long-term spatial memory are assessed by varying the interval between exposure trials, and between the last exposure trial and the test trial. **e** | A memory index (reflecting novelty preference in terms of time spent in arms) showed that *Gria1*$^{-/-}$ mice exhibit impaired short-term spatial memory but enhanced long-term spatial memory. The red line in the inset of part **b** and in part **e** indicates chance performance. Part **b** is reproduced, with permission, from REF. 129 © (2002) Macmillan Publishers Ltd. All rights reserved. Part **c** is reproduced, with permission, from REF. 20 © (2003) Society for Neuroscience. Parts **d** and **e** are reproduced, with permission, from REF. 10 © (2009) Cold Spring Harbor Laboratory Press.

during which the platform and beacons were removed from the pool; see FIG. 3b), they were more likely to choose the incorrect, decoy beacon and made more errors overall (FIG. 3a). This deficit was primarily seen for trials in which the starting position of the mice was close to the decoy beacon (S^- trials) (FIG. 3c). *Grin1*$^{\Delta DGCA1}$ mice were unable to stop themselves from swimming to the nearest beacon on trials when this was the wrong thing to do. Importantly, this is not a memory encoding problem. In a subsequent beacon water maze study, mice were trained to discriminate between the two visually identical beacons, depending on their allocentric spatial locations, but this time, all of the trials started from either of the two equidistant start positions. There was no deficit in spatial discrimination in the *Grin1*$^{\Delta DGCA1}$ mice during this acquisition phase. However, their spatial discrimination was then subsequently impaired during probe trials starting from a point close to the decoy beacon (S^- trials)[52]. Thus, *Grin1*$^{\Delta DGCA1}$ mice are unable to use the spatial information provided by the extramaze cues to inhibit a conditioned, but inappropriate, behavioural tendency to approach any beacon that looks correct.

In a non-spatial visual discrimination version of the task, in which two visually distinct beacons (for example, a black-and-white striped cylinder versus a grey funnel) and multiple start locations were used, the *Grin1*$^{\Delta DGCA1}$ mice showed no impairments in discrimination performance, even on trials starting from a point close to the incorrect beacon (FIG. 3d,e). This dissociation between spatial and non-spatial (visual) discrimination performance in *Grin1*$^{\Delta DGCA1}$ mice does not simply reflect the presence or absence of a spatial component. *Grin1*$^{\Delta DGCA1}$ mice are, after all, capable of learning the spatial location of the platform (see also FIG. 2b). Instead, the dissociation may result from the inherent ambiguity that is present in the task when using visually identical beacons but that is not present in the version of the task using visually distinct beacons. There is no deficit when unambiguous, non-overlapping visual stimuli are used. By contrast, during performance of the spatial discrimination task with two visually identical beacons, mice will form two distinct memories associated with the beacon (beacon means escape and beacon means no escape), and so the beacon is an ambiguous cue. The mice must therefore use the spatial cues as a conditional cue or occasion setter to decide whether a particular beacon should be approached or avoided. *Grin1*$^{\Delta DGCA1}$ mice are unable to disambiguate between these competing or

overlapping memories associated with the visually identical beacons. A similar account could explain the preferential effects of hippocampal lesions on contextual fear conditioning compared with cue (for example, tone) conditioning[53] (see REF. 54 for review). This dissociation, which is often observed, may not reflect the spatial versus non-spatial nature of the cues but rather the greater ambiguity and uncertainty that is associated with the context. Whereas the cue is always followed by shock, the context is an ambiguous predictor because it is present not only when the shock is given but also in the absence of the shock[55].

Re-appraising the role of the hippocampus in pattern separation. The inability to disambiguate between overlapping memories could be considered as a pattern separation failure. Pattern separation is the ability to distinguish between similar or overlapping inputs. Computational models have suggested a role for the hippocampus, and in particular the dentate gyrus, in pattern separation[56–61]. This has generally been interpreted in terms of the ability to distinguish between spatial inputs, resulting from the overlap of extramaze spatial cues. However, empirical evidence in support of this theory is limited and has so far come from a small number of lesion studies in rats and experiments in genetically modified mice. Dentate gyrus lesions that are restricted to dorsal hippocampus have been shown to produce deficits in SWM during a delayed matching-to-place, open-field cheeseboard task. Importantly, the impairment was only evident when the two spatial locations that were to be discriminated were close together, thus presumably maximizing the need for pattern separation[62]. Studies using genetically modified mice have also supported a role for NMDARs in dentate gyrus granule cells in pattern separation in a contextual fear-conditioning paradigm in which mice were required to discriminate between two similar contexts[63]. More recently, it has also been suggested that the variable behavioural effects of ablating adult neurogenesis in the dentate gyrus that are seen across numerous studies may be explained by the role of these new neurons in pattern separation and the variable requirement for pattern separation in the different memory tasks used in different studies[64] (but see also REF. 65).

However, the SRM impairment in the radial maze task in *Grin1*$^{\Delta DGCA1}$ mice is independent of the spatial separation between the arms of the maze[33,51] (FIG. 2c). Furthermore, the various water maze results demonstrate that *Grin1*$^{\Delta DGCA1}$ mice can successfully discriminate between, and use the extramaze spatial cues. Instead, our data identify a quite different ambiguity or overlap that leads the mice to select the wrong arms on the radial maze. This derives from the intramaze cues that are common to all of the arms (that is, all the arms have the same physical appearance) and that have become partially associated with reward. To show successful discrimination between the always-rewarded and never-rewarded arms, the mice must inhibit the tendency to run down the never-rewarded arms. They must use the extramaze spatial cues to select the correct response (run versus do not run) for each arm, just as they have to select between approaching or avoiding the beacons in the spatial discrimination water maze task. *Grin1*$^{\Delta DGCA1}$ mice are unable to pattern separate the 'arm–food' and 'arm–no food' memories (or separate the 'beacon–escape' memory from the 'beacon–no escape' memory). Thus, hippocampal pattern separation supports discrimination between overlapping memories or behavioural goals rather than discrimination between extramaze spatial cue clusters.

The role of hippocampal NMDARs in spatial reversal and the delayed-matching-to-place task. Therefore, a key role of hippocampal NMDARs lies in selecting between competing and conflicting memories and between the different behavioural response choices that these memories support. Equally, a role in resolving conflict or ambiguity could underlie other spatial memory deficits resulting from hippocampal NMDAR dysfunction. For example, AP5-treated rats show impairments during spatial reversal testing in the water maze when, after an initial period of drug-free pre-training to one spatial location, the platform is then moved to a novel location in the same familiar environment[66]. In this task, animals are pre-trained as normal animals on a standard SRM version of the water maze task, exactly as they are in the spatial pre-training condition described in the upstairs–downstairs task[38]. However, rather than being tested with AP5 on the acquisition of a second reference memory task in a different water maze environment, these animals are now trained to find a new platform location in the same, familiar spatial environment. The spatial reversal impairment with AP5 is in marked contrast to the lack of effect on the upstairs–downstairs task. Thus, the requirement for NMDARs is greater when an animal is required to learn a new goal location within a familiar environment compared with learning an entirely new spatial layout. *Grin1*$^{\Delta DGCA1}$ mice also show impairments in spatial reversal in the water maze[33] (FIG. 2b). The water maze reversal paradigm generates conflict and ambiguity between the old and new platform locations. Notably, the deficit in *Grin1*$^{\Delta DGCA1}$ mice during spatial reversal testing reflects

Box 2 | GluA1 and short-term memory

The GluA1 subunit is thought to have an important role in aspects of AMPA receptor trafficking[135,136] and in mechanisms underlying synaptic plasticity, particularly short-term forms of plasticity[130,137–139]. GluA1 is also important for spatial working memory (SWM) performance[20,129,140]. To perform well on SWM (win–shift maze) tasks animals must avoid recently visited arms (which are relatively more familiar) and select currently more novel arms when given a choice. This reduced preference for familiar locations and increased preference for more novel locations reflects innate foraging behaviour and does not require any rule to be learned; animals will win–shift spontaneously. It does, however, require the ability to judge the moment-to-moment relative familiarity of the arms of the maze. *Gria1*$^{-/-}$ mice (which lack the gene encoding the GluA1 AMPA receptor subunit) have an impaired ability to represent familiarity on the basis of recent experience[10,141–143]. Thus, the key psychological process that is disrupted in *Gria1*$^{-/-}$ mice, and which underlies their SWM deficit, is stimulus-specific, short-term habituation[11]. This short-term memory deficit is in marked contrast to the normal, or even enhanced, long-term spatial memory exhibited by *Gria1*$^{-/-}$ mice[10,20,129,130]. In fact, it is the absence of short-term memory in *Gria1*$^{-/-}$ mice that can account for the facilitation of long-term spatial memory in these animals. Long-term associative memories are formed best when the stimuli involved are surprising and capture a lot of attention (for example, if they have not been presented recently). Thus, new associative learning is slower for familiar stimuli. In wild-type mice, this short-term memory process, which is non-associative and provides a sense of familiarity (and hence a lack of surprise), actually limits associative long-term memory formation. The absence of short-term memory in *Gria1*$^{-/-}$ mice can lead to the formation of stronger long-term memories. Thus, GluA1-dependent short-term memory and GluA1-independent long-term memory are two parallel memory processes that, depending on the conditions, can interact or compete with each other. It is important to note therefore that these short-term memories are not serially converted into long-term memories. These findings are explained by an enduring model of animal learning[126,144,145].

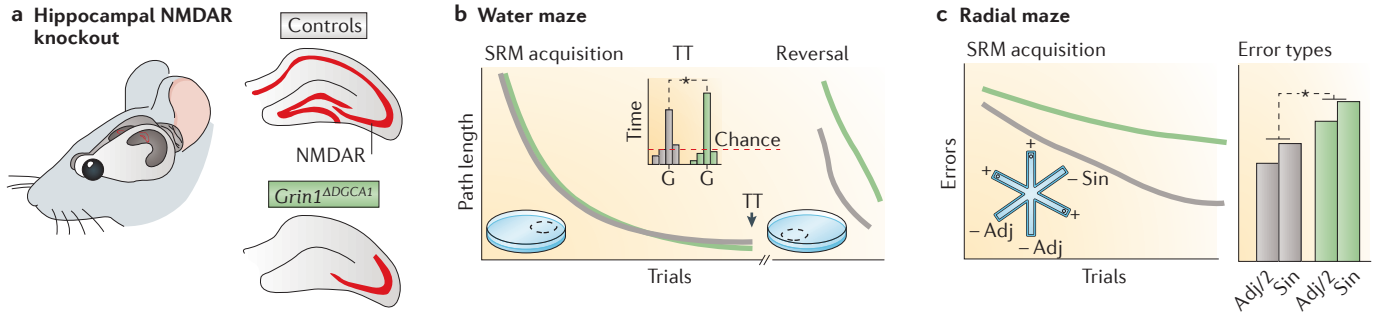

Figure 2 | **Impaired spatial reference memory on the radial maze but normal spatial reference memory in the open-field water maze in *Grin1*$^{\Delta DGCA1}$ mice.** **a** | Hippocampal NMDA receptor (NMDAR) expression in mice lacking the gene encoding the GluN1 NMDAR subunit in dentate gyrus granule cells and CA1 pyramidal cells (*Grin1*$^{\Delta DGCA1}$ mice) and in control mice. **b** | Control and *Grin1*$^{\Delta DGCA1}$ mice acquired the spatial reference memory (SRM) version of the water maze at a similar rate. They exhibited similar path lengths to find a hidden escape platform in a fixed spatial location (shown as a dashed circle) during acquisition training. *Grin1*$^{\Delta DGCA1}$ mice actually spent more time searching in the goal (G) quadrant (that is, the quadrant that normally contains the platform) during the transfer test (TT) conducted at the end of acquisition training, during which the platform is removed from the pool and the mice were allowed to swim freely for 60 seconds (see inset, where each bar on the histogram represents time spent in a quadrant of the pool). However, in *Grin1*$^{\Delta DGCA1}$ mice, performance was impaired when the platform was then moved to the diametrically opposite position in the water maze (reversal). **c** | *Grin1*$^{\Delta DGCA1}$ mice were impaired on the SRM radial maze task compared with control mice. Mice were trained to discriminate between arms of the radial maze that contained a food reward (+ arms) and arms that were never rewarded (– arms). The never-rewarded arms were arranged so that there was a single (Sin) spatially isolated, non-rewarded arm, and two spatially adjacent (Adj) non-rewarded arms; entry into a never-rewarded arm constituted an SRM error. Note, mice were prevented from making SWM errors during SRM acquisition. *Grin1*$^{\Delta DGCA1}$ mice made more SRM errors than control mice during acquisition. Regarding 'error types', the SRM impairment in *Grin1*$^{\Delta DGCA1}$ mice is as clear for the single arms as it is for the adjacent arms[33,51]. *Grin1*$^{\Delta DGCA1}$ mice made more SRM errors than control mice into both single and adjacent non-rewarded arms. The asterisks indicate a statistically significant difference. Figure is reproduced, with permission, from REF. 33 © (2012) Macmillan Publishers Ltd. All rights reserved.

their increased perseveration to the old platform location. This is evident by the greater time spent in the training quadrant during the transfer test (which was performed in extinction) conducted at the end of the initial water maze acquisition training (FIG. 2b; see also REF. 67).

Likewise, the delayed-match-to-place SWM version of the water maze task, during which the platform is moved to a novel position on each day of testing, could be considered as a daily sequence of new spatial reversal tasks. AP5-treated rats show impaired performances on this task[68], as do mice in which NMDARs have been ablated from the CA3 subfield[69]. Integral to successful performance on the delayed-match-to-place task is the ability to detect and resolve the conflict between currently valid and previously valid platform locations, and to behaviourally inhibit the response to go back to previous platform locations. Thus, the performance deficits that occur following blockade or ablation of hippocampal NMDARs on the spatial reversal and delayed-match-to-place tasks may not be due to a failure in the rapid encoding of new spatial memories but rather may reflect an inability to resolve the conflict that arises when goal locations are changed coupled with an inability to behaviourally inhibit spatial responses that are now no longer appropriate.

Extra-hippocampal NMDARs and long-term spatial memory. Thus NMDARs in the hippocampal CA1 subfield are not required for encoding and/or storing associative long-term spatial memories[33]. Note also that ablation of NMDARs from either the dentate gyrus alone or from CA3 does not impair SRM acquisition in the water maze[63,70]. How then are these memories encoded? It remains possible that other NMDAR-independent forms of synaptic plasticity in the hippocampus could support long-term spatial memory[71]. However, it may not be the NMDAR-dependent LTP-dependent memory hypothesis that is wrong but rather the role of the hippocampus that needs to be re-examined.

The more general form of the hypothesis that NMDAR-dependent synaptic plasticity underlies associative long-term spatial memory may still be correct. It would be a mistake to overlook the many studies in genetically modified mice that have reported a positive correlation between impairments in LTP and impairments in spatial memory performance[72]. Furthermore, the properties of NMDAR-dependent LTP that make this plasticity attractive as a cellular model of associative learning still apply[25,26]. The same reasoning that led people to propose NMDAR-dependent synaptic plasticity in the hippocampus as the neural substrate of long-term spatial memory could equally suggest that NMDAR-dependent synaptic plasticity elsewhere in the brain subserves this function now that we have shown that NMDARs in the hippocampus are not required.

In fact, there is considerable evidence that extra-hippocampal NMDARs play an important part during the acquisition phase of the SRM water maze task. The performance of conditional *Tg29-1 Grin1*-knockout mice was, after all, impaired during the acquisition phase of the standard SRM version of the water maze task, although the performance was also mildly impaired on the visible platform task[45]. Taken in combination with the absence of an impairment in water maze learning in the hippocampus-specific *Grin1*$^{\Delta DGCA1}$ mice[33], these data demonstrate that extra-hippocampal NMDARs make an important contribution to associative long-term spatial memory. A similar conclusion can be reached by comparing studies in conditional NMDAR-GluN2B-subunit-knockout mice. Whereas ablation of the GluN2B subunit in both the hippocampus and cortex impaired water maze learning[49] (but importantly had no effect on the visible platform control task), deletion restricted to just the hippocampus had no effect[67]. Thus, these data demonstrate that NMDARs either elsewhere in the extended hippocampal formation, such as the entorhinal cortex[73] or subiculum[5], or across the wider cortical mantle, are necessary for spatial memory performance. This should hardly come as a surprise.

Implications for theories of hippocampus

So maybe what needs to be reconsidered is the role of the hippocampus. The results from *Grin1*$^{\Delta DGCA1}$ mice have important implications for current theories of hippocampal function. In light of these results, what does the hippocampus really do?

Beyond the spatial memory domain. Hippocampal lesions have well-documented effects on spatial memory task performance, but alongside these there are numerous examples of hippocampal lesions also affecting performance on non-spatial memory tasks[74–79]. Furthermore, there is considerable evidence that the hippocampus has a role beyond the memory domain altogether. Indeed, the hippocampus has long been associated with aspects of emotionality and, in particular, with anxiety[80–82]. In recent years, interest in the hippocampus and emotionality has been rekindled, particularly in light of the suggestion that adult hippocampal neurogenesis might play an important part in aspects of emotionality and in mediating the action of antidepressant drugs[83] (but see also REF. 84). Hippocampal lesions also reduce anxiety in a number of different ethological unconditioned paradigms such as the elevated plus maze[85,86] that include no explicit role at all for prior learning (and hence competing memories). Furthermore, both pharmacological antagonism and genetic ablation of hippocampal NMDARs are also anxiolytic[51,87].

Over the past decade, it has become increasingly clear that the spatial memory and anxiety functions of the hippocampus are preferentially associated with its dorsal subregions (posterior hippocampus in primates; also known as the septal pole) and ventral subregions (anterior hippocampus in primates; also known as the temporal pole), respectively (FIG. 4). Although the internal circuitry of the hippocampus is remarkably regular along its septotemporal axis, the extrinsic connectivity is very different for the dorsal and ventral subregions[88–91]. Whereas the dorsal hippocampus receives highly processed, polymodal sensory information from cortical areas, the ventral hippocampus is much more closely linked to subcortical structures such as the amygdala, and the hypothalamus–pituitary–adrenal (HPA) axis.

Functionally, this is reflected in a double dissociation between the effects of selective fibre-sparing dorsal and ventral hippocampal lesions. Whereas dorsal lesions impair performance across a wide range of spatial memory tasks, ventral lesions have very little, if any, effect on spatial memory task performance[75,92–96]. By contrast, ventral but not dorsal hippocampal lesions have been found to reduce anxiety on a number of ethologically based, unconditioned tests, including the widely used elevated plus maze and novelty-suppressed feeding tests[95,97–101]. This double dissociation between the effects of dorsal hippocampal lesions on spatial memory and ventral hippocampal lesions on anxiety is important because it means that the effects of hippocampal lesions on anxiety cannot be explained simply in terms of spatial memory impairments. Ventral hippocampal lesions have also been reported to affect emotional behaviour during conditioned tests such as contextual freezing, although this is more contentious[97,102,103]. It is also important to point out that the effects of ventral hippocampal lesions are not limited to aversive tests of emotionality[75,104]. Furthermore, similar dissociations of function along the septotemporal axis of the human hippocampus have also been reported. Functional and structural imaging studies have suggested a preferential role for septal pole of the hippocampus in spatial navigation and memory, whereas the temporal pole is again associated with emotional processing[8,82,105–109]. More recently, the possibility of another distinct functional zone within the hippocampus has been suggested, which corresponds to the intermediate subregion[110,111].

A common algorithm. Nevertheless, despite this double dissociation, the consistent internal anatomical organization along the septotemporal axis of the hippocampus suggests that behaviour in both spatial memory tasks and anxiety tests may depend on a common hippocampal algorithm or operation performed throughout the dorsal and ventral subregions, respectively, but acting on their different inputs and outputs. There is the same repeating lamellar organization, with the same characteristic trisynaptic circuitry, throughout the whole hippocampus. Furthermore, any account of hippocampal function that aims to be more than merely partial must explain not only its role in spatial memory but also its role in anxiety. So what is the common algorithm being performed by the hippocampus, and can our results with *Grin1*$^{\Delta DGCA1}$ mice provide more information about the identity of this process (or processes)?

What is anxiety? Before considering the nature of this algorithm, it is worth first describing precisely what is meant by anxiety. Anxiety is primarily a response to potential danger, and it has evolved in order to prevent the organism from going into potentially dangerous situations. Anxiety is considered to be distinct from fear, which is the response to imminent danger, and different neural circuits are involved in these different protective or defensive behaviours[80,81]. Anxiety is associated with conflict or uncertainty, and it arises when there is competition between concurrently available goals or response choices. This can arise through various routes: for example, there is conflict between potential unlearned outcomes in simple, ethological unconditioned laboratory tests of anxiety, such as the elevated plus maze. Such tests are based on an approach versus avoidance conflict, with the animal being required to choose whether to explore the open, exposed arms of the maze, which are potentially dangerous but also potentially rewarding (approach), or to stay in the safe, enclosed sections (avoidance).

Gray[80], and subsequently Gray and McNaughton[81], suggested that a neurobiological system mediating anxiety must respond to situations of conflict or uncertainty and, once activated, evoke a constellation of responses in order to resolve that conflict. This involves increasing arousal levels, modulating attentional processes in order to change the salience of stimuli in the environment and, importantly, suppressing ongoing motor programmes (behavioural inhibition). Furthermore, Gray[80] suggested

Box 3 | **Mice lacking NMDARs in the dentate gyrus**

Genetically modified mice lacking the gene encoding the GluN1 subunit, and hence NMDA receptors (NMDARs), specifically in dentate gyrus granule cells have also been generated (*Grin1*$^{\Delta DG}$ mice)[51,63]. These mice have normal NMDAR expression levels in CA1 and CA3 pyramidal cells. They do, however, exhibit comparable dentate gyrus granule cell loss to the *Grin1*$^{\Delta DGCA1}$ mice (which lack *Grin1* in dentate gyrus granule cells and CA1 pyramidal cells) (Y. Watanabe, P.H.S. and H.M., unpublished observations). Crucially, the behavioural phenotype of these *Grin1*$^{\Delta DG}$ mice is much reduced from that seen in the *Grin1*$^{\Delta DGCA1}$ mice. In particular, their acquisition of spatial reference memory is not impaired in the radial maze task[51] (which is dramatically impaired in the *Grin1*$^{\Delta DGCA1}$ mice; see FIG. 2c). Importantly, this therefore demonstrates that the ablation of NMDARs in CA1 must have at least some role in the behavioural deficit in the *Grin1*$^{\Delta DGCA1}$ mice. Notably, the performance of *Grin1*$^{\Delta DG}$ mice is impaired on the spatial working memory component of the radial maze task.

that it is the hippocampal system that subserves these functions. Our data have re-energized this idea.

The idea that the hippocampus might be a key component of a comparator system to detect conflict or uncertainty is far from new[80,81,112]. Furthermore, the idea of the hippocampus as part of a behavioural inhibition system pre-dates even the cognitive map hypothesis[113–117]. Importantly, this view does not identify the hippocampal comparator system as a reward prediction error signal that retrospectively determines the extent of associative learning on the basis of reinforcing outcomes[118,119]. Instead, the key outputs of this hippocampal comparator are prospective changes in attention and arousal processes that could influence subsequent learning[120,121] and the activation of a behavioural inhibition system to suppress current motor actions[81]. The dependence of the memory deficit in *Grin1*$^{\Delta DGCA1}$ mice in the spatial discrimination water maze task on the start position of the trials (FIG. 3c) demonstrates the role of the hippocampus as part of a behavioural inhibition system, which is required when there is a conflict or ambiguity between simultaneously retrieved associative memories that differ in their implications as to whether to approach or avoid the nearest beacon.

This hypothesis could equally be extended to previous studies that have emphasized the role of the hippocampal comparator when mismatch occurs because the current state of the perceptual world differs from what would have been expected based on long-term memory. Evidence from human fMRI studies[120,122,123], and both electrophysiological studies[124,125] and lesion studies in rodents[79,126,127], have implicated the hippocampus, particularly the CA1 subfield, in the response to associative mismatch and conflict of this kind. For example, rats exposed to two separate audiovisual sequences (for example, a tone followed by a constant light or a click followed by a flashing light) will learn these sequences and habituate to the cues. However, if the auditory cues that precede the visual stimuli are switched (that is, a tone followed by a flashing light or a click followed by a constant light), then normal rats will exhibit renewed orienting to the lights. This is not the case for rats with hippocampal lesions, suggesting that these animals are unable to respond appropriately to the associative mismatch that occurs when an expectation based on information retrieved from long-term memory conflicts with the current sensory reality[127]. Analogous experimental designs involving sequences of visual stimuli have also revealed hippocampal activation in response to associative mismatch in human fMRI studies[123]. Potentially consistent with this, the performance of *Grin1*$^{\Delta DGCA1}$ mice is impaired (FIG. 2b) in the standard open-field water maze task when the platform is moved to the diametrically opposite location in the pool (a form of spatial reversal)[33], suggesting that these mice likewise fail to respond normally to a mismatch between retrieved information and actual current experience. It would be interesting to see whether the increases in CA1 pyramidal cell firing seen in rats in response to changes in the goal location in a familiar spatial environment[125], which could be a neuronal index of mismatch detection, could be prevented by NMDAR deletion in *Grin1*$^{\Delta DGCA1}$ mice. Thus,

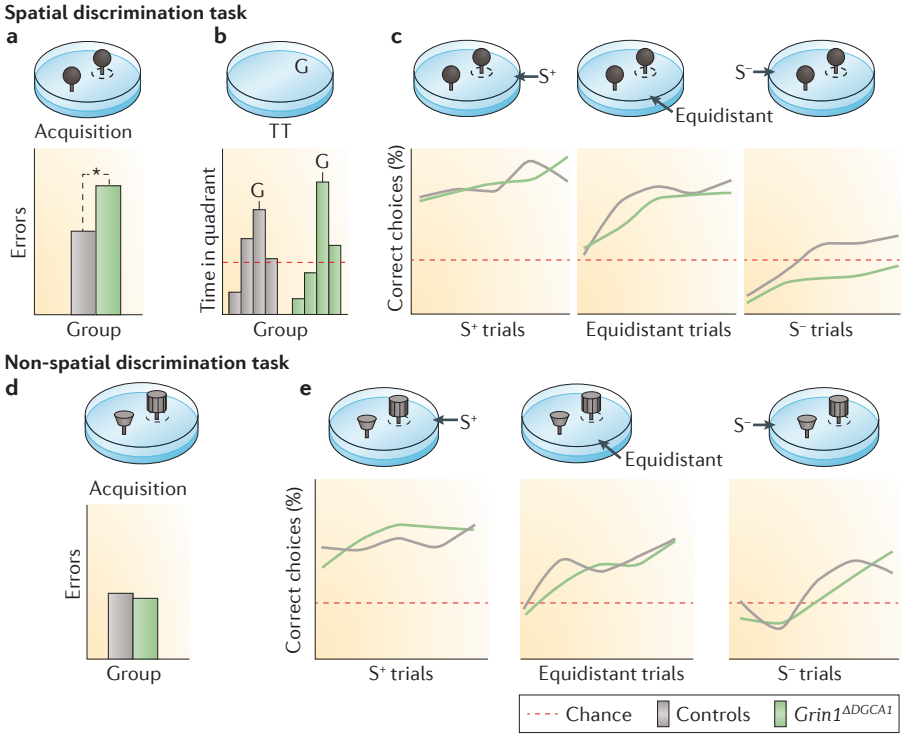

Figure 3 | **Impaired spatial discrimination but normal non-spatial discrimination in the water maze in the *Grin1*$^{\Delta DGCA1}$ mice.** Control mice and mice lacking the gene encoding the GluN1 NMDA receptor subunit in dentate gyrus granule cells and CA1 pyramidal cells (*Grin1*$^{\Delta DGCA1}$ mice) were compared on both a spatial discrimination and a non-spatial discrimination beacon task in the Morris water maze[33]. **a**,**b** | In the spatial discrimination task, there were two visually identical beacons (black spheres) sitting on the water surface, only one of which indicated the position of the fixed-location, hidden escape platform (indicated by the dashed circle). The correct and decoy beacons were differentiated solely by their allocentric spatial locations relative to the extramaze room cues. *Grin1*$^{\Delta DGCA1}$ mice were much more likely to choose the wrong beacon than control mice and made more errors during the acquisition phase of the task (part **a**). This was despite showing an equivalent, strong preference for the goal (G) quadrant (that is, the quadrant that normally contains the platform) during a transfer test (TT) conducted at the end of training (part **b**). Each bar on the histogram represents the time spent in a quadrant of the pool. **c** | During the acquisition phase of the spatial discrimination task, trials started at the edge of the pool, pseudorandomly either from a point close to the correct beacon (S^+ trials), from a point close to the incorrect, decoy beacon (S^- trials) or from a point equidistant between the two beacons. The deficit in discrimination performance in *Grin1*$^{\Delta DGCA1}$ mice was primarily due to a poorer performance (that is, a lower percentage of correct choices) than control mice on trials that were started from a point close to the decoy beacon (S^- trials). **d** | In the non-spatial visual discrimination task, the mice were required to choose between two visually distinct beacons (a funnel versus a cylinder), the spatial locations of which were moved randomly from trial to trial. The platform (indicated by the dashed circle) was always associated with one particular beacon (for example, the cylinder) for a given animal. Control mice and *Grin1*$^{\Delta DGCA1}$ mice made a similar number of choice errors on the non-spatial version of the task. **e** | During the acquisition phase of the non-spatial discrimination task, trials started at the edge of the pool, pseudorandomly either from a point close to the correct beacon (S^+ trials), from a point close to the incorrect, decoy beacon (S^- trials) or from a point equidistant between the two beacons. There was no difference in choice accuracy between *Grin1*$^{\Delta DGCA1}$ mice and control mice from any of the start positions (as reflected by the percentage of correct choices). The red dashed lines in parts **b**, **c** and **e** indicate chance performance. Figure is reproduced, with permission, from REF. 33 © (2012) Macmillan Publishers Ltd. All rights reserved.

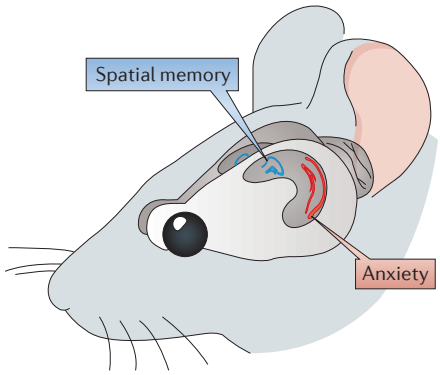

Figure 4 | **Distinct contributions of the dorsal and ventral hippocampus to behaviour.** Subregion specific, cytotoxic lesions have fractionated the hippocampus in terms of their behavioural effects. The dorsal hippocampus (posterior hippocampus in primates) subserves the spatial memory functions of the hippocampus (for example, in the water maze and radial maze), whereas the ventral hippocampus (anterior hippocampus in primates) underlies the anxiolytic effects of hippocampal lesions (for example, on the elevated plus maze).

the hippocampal comparator may play an important part not only when there is interference between competing or overlapping long-term memories but also when the current state of the world conflicts with what is expected based on long-term memory.

Role of place cells. So what is the role of place cells? Although cells in the hippocampus are capable of responding to spatial information, it is still not clear precisely what information is being conveyed when a place cell fires, nor how this information is used to perform hippocampus-dependent spatial memory tasks such as the water maze or the radial maze. Single-unit recording studies alone cannot demonstrate the causal roles of the activity that they monitor. Furthermore, recent studies of hippocampal unit activity in genetically modified mouse lines suggest that the fidelity of the relationship between the place cell and its place field, and spatial memory abilities on behavioural tasks such as the water maze and radial maze is not straightforward. For example, Resnik *et al.*[128], recently reported that place cells recorded in the dorsal CA1 region are substantially disrupted in mice lacking GluA1-containing AMPARs throughout the brain. Large reductions were found in all measures of spatial and directional selectivity; the accuracy of the population code was substantially reduced, and the absolute representation of space was greatly diminished. Despite this, SRM in the water maze and radial maze tasks is unimpaired in mice lacking GluA1 (REFS 20,129,130) (FIG. 1b,c). In line with a hypothesis that the hippocampus acquires and encodes spatial information, it has been argued that the residual spatial coding in GluA1-lacking neurons may still be sufficient to perform SRM tasks and that, taken across the entire neuronal population, the decoding accuracy is still far better than chance levels[128]. It has also been argued that SRM tasks might just be less sensitive than SWM tasks and that working memory performance may be particularly sensitive to place cell disruption because working memory requires a flexible representation of position that is rapidly modified by trial-specific information. However, it is important to point out that long-term spatial memory can actually be enhanced in these GluA1-lacking mice[10,20] (FIG. 1c,e). Therefore, the dissociation between short- and long-term spatial memory performance in these mice cannot be due to differences in task sensitivity. Furthermore, it is hard to see how the cognitive map hypothesis, as it stands, could explain why a reduction in spatial information processing in CA1 place cells would actually lead to enhanced long-term spatial memory.

It is also of note that mutants with genetic manipulations that are restricted to GABAergic interneurons routinely exhibit a behavioural phenotype of impaired SWM and/or short-term memory but normal SRM (BOX 4). Despite this, differences between these mutants at the cellular and network level are quite remarkable. For instance, mice that lack NMDARs in parvalbumin-positive GABAergic neurons throughout the brain and mice that do not express connexin 36 (also known as GJD2) exhibit reduced spatial and temporal coding[131,132]. However, in mice lacking GluA4 subunit-containing AMPARs, specifically in hippocampal parvalbumin-positive interneurons, temporal coding is impaired, whereas spatial coding remains intact[133]. Although any one of the disturbances identified in the different mutants with genetic modifications in GABAergic interneurons might suffice to hamper processes supporting SWM, none seems to be essential for long-term SRM.

Therefore, further experiments are required to fully understand the relationship between place cell activity (including both spatial and temporal coding) and performance on different spatial memory tasks. In addition, it will also be important to test the causal role of other cell types, such as grid cells in the entorhinal cortex, in performance on spatial memory tasks. Moreover, any unifying account of hippocampal function must explain the contribution that hippocampal pyramidal cell firing within the different hippocampal subfields makes not only to spatial but also to non-spatial memory tasks, and to anxiety.

Conclusions

Recent studies in *Grin1*$^{\Delta DGCA1}$ mice challenge the long-standing belief that long-term spatial memories are encoded in the CA1 subfield of the hippocampus through an NMDAR-dependent LTP-like mechanism. We argue that it may not be the NMDAR-dependent synaptic plasticity-dependent memory hypothesis that is wrong but rather that the role of the hippocampus needs to be

Box 4 | **GABAergic interneurons and spatial memory**

Studies using genetically modified mice have highlighted the crucial role of GABAergic interneurons in specific aspects of spatial information processing at the network and behavioural levels. Selective AMPA receptor subunit ablations restricted just to GABAergic interneurons[146] have shown that GluA1 in parvalbumin-positive interneurons and also GluA4 preferentially expressed in parvalbumin-positive interneurons are required for spatial working memory (SWM) but are not required for spatial reference memory (SRM). In fact, the SWM deficit in mice lacking GluA1 in parvalbumin-positive interneurons is almost as pronounced as that reported for mice with global GluA1 deletion. Ablation of the GluN1 subunit of the NMDA receptor from parvalbumin-positive interneurons of the forebrain is also associated with a SWM deficit, again leaving SRM intact[131]. Maybe even more interestingly, ablation of gap junction coupling between interneurons recapitulates this same behavioural phenotype[132]. Thus, interfering with interneuron activity ensures dissociation between SWM and SRM. This hypothesis has been further strengthened using cell type-specific and region-specific genetic manipulations. Thus, reducing either the input[133] or output[147] of hippocampal parvalbumin-positive interneurons by virus-mediated manipulations leads to selective SWM deficits that are comparable with those reported in mice with global GluA1 deletions. One may not have expected these SWM deficits if one considers that GABAergic interneurons constitute maximally 10–20% of all neurons in the forebrain, but the behavioural deficit is less surprising if one considers that GABAergic interneurons are the major cell type ensuring a range of distinct oscillatory activities that are considered to be a prerequisite for numerous cognitive processes, including learning and memory[148–150]. What is surprising is what little effect, if any, disrupting interneuron function seems to have on SRM.

re-examined. Extra-hippocampal NMDARs play an important part in spatial learning, which is consistent with the possibility that NMDAR-mediated currents during basal synaptic transmission and/or NMDAR-dependent synaptic plasticity outside the hippocampus contribute to associative spatial memory formation.

We propose that hippocampal NMDARs have a crucial role within a comparator–behavioural inhibition system for detecting and resolving conflict or uncertainty, such as that which might occur between ambiguous or overlapping memories, or between competing behavioural goals (for example, during anxiety tests). It has previously been suggested that the hippocampus may have a key role in integrating information about motor actions or response choices that are being taken towards achieving a specific goal with information about the current state of the sensory world[134]. However, whereas this previous model has emphasized a conjunctive code in which a configural representation is formed by mixing these different kinds of information, we suggest that sensory stimuli act as occasion-setting cues to enable the correct motor action or response choice to be selected when there is competition between concurrently available goals or response choices. A key avenue for future research is to determine how these psychological processes map onto the electrophysiological signatures of the various subfields of the hippocampus and its neighbouring structures.

Finally, human episodic memories might be particularly dependent on such a system for their accurate retrieval, given that there is likely to be a high degree of ambiguity or overlap from one such memory to the next. By contrast, semanticized memories, by their very nature, provide a unique identifier, which enables highly efficient retrieval. Ultimately, the role of the hippocampus in memory must be integrated within a unifying model of hippocampal function that also explains its role in anxiety[81].

David M. Bannerman, Stephen B. McHugh and J. Nicholas P. Rawlins are at the Department of Experimental Psychology, University of Oxford, Oxford, OX1 3UD, UK.

Rolf Sprengel and Peter H. Seeburg are at the Max Planck Institute for Medical Research, D-69120 Heidelberg, Germany.

David J. Sanderson is at the Department of Psychology, Durham University, Durham, DH1 3LE, UK.

Hannah Monyer is at the Department of Clinical Neurobiology, Medical Faculty of Heidelberg University and German Cancer Research Center (DKFZ), Heidelberg 69120, Germany.

Correspondence to P.H.S. and D.M.B.
e-mail: Peter.Seeburg@mpimf-heidelberg.mpg.de; david.bannerman@psy.ox.ac.uk

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The authors declare no competing interests.