Hippocampal synaptic plasticity, spatial memory and anxiety

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Abstract

Recent studies with transgenic mice lacking NMDARs in the hippocampus challenge head-on the longstanding hypothesis that hippocampal LTP-like mechanisms underlie the encoding and storage of associative, long-term spatial memories. However, it may not be the synaptic plasticity/memory hypothesis that is wrong. Instead, it may be the role of the hippocampus that needs re-examination. We present an account of hippocampal function which explains its role in both memory and anxiety.

Introduction

The ability to learn and remember spatial locations, and to associate them with other stimuli, is an essential adaptive behaviour 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] (see BOX 1), the observation of place cells in rodents[7], and more recently from fMRI studies in humans[8,9]. However, these approaches are limited in that they typically provide little information about the psychological, synaptic and molecular mechanisms that underlie spatial information processing and thus, they represent only a limited tool for understanding spatial learning and memory.

By contrast, studies with genetically altered mice in which NMDARs and AMPARs have been selectively manipulated, have generated striking dissociations within spatial memory, revealing important information as to the psychological processes that underlie performance on different spatial memory tasks. For example, studies with mice lacking the GluA1 subunit of the AMPAR (*Gria1*$^{-/-}$ mice) have revealed clear dissociations between spatial working memory (SWM) and spatial reference memory (SRM; Figure 1), indicating 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 with hippocampus-specific NMDAR knockout mice (*Grin1*$^{\Delta DGCA1}$ mice) have even revealed dissociations between different SRM tasks (between watermaze and radial maze; BOX 1), which challenge long-standing views about the importance of hippocampal synaptic plasticity, in particular long-term potentiation (LTP), for the encoding and storage of associative, long-term spatial memories. In this article, we will 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 plays 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, comprising information from different sensory modalities. Some spatial tasks can be solved

on the basis of 'egocentric' (self-centered) information (e.g. 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-centered') 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 (e.g. if it is forced to leave a customary route and find a new way home).

O'Keefe and Nadel proposed that there are two distinct systems that guide spatial learning and memory[1]. The first of these, the 'taxon' system, uses egocentric cues and specific behavioural responses to specific landmarks or stimuli to allow for route-based navigation (e.g. always turn right, always approach stimulus X, always move away from stimulus Y, etc.). 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 hypothesised that this cognitive map is maintained in the hippocampus with place cells as its basic functional units[1]. O'Keefe and colleagues found cells in the hippocampus of behaving rats that 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 variety of tasks including the Morris watermaze,[4,5] the radial maze[3,20], T-maze rewarded alternation[6], and many others (see BOX 1). Indeed, the hippocampus plays an important role in allocentric spatial information processing in a great many species, including humans[2,8,9].

Synaptic plasticity and spatial memory formation

It is of course essential to be able to associate particular spatial locations, within an environment or cognitive map, with particular events or outcomes, such as reward or danger. It has 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 (i.e. associating particular spatial locations within a cognitive map with particular events or 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 long-term, associative spatial memory formation[33].

NMDAR-dependent synaptic plasticity and associative, long-term spatial memory

The role of hippocampal NMDARs in spatial reference memory tasks

The induction of the most commonly studied form of LTP depends on 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]. This has become firmly established in the textbooks.

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 taken in which the effects of NMDAR antagonists such as AP5, which block the induction of LTP, were assessed on spatial learning and memory. Second, genetically modified mice lacking NMDARs in specific brain regions and neuronal cell types have also been 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 will first briefly review these older studies before then describing data from a novel genetically modified mouse line from which stronger conclusions can be drawn.

NMDAR antagonists and spatial learning

Morris and colleagues showed that blocking NMDARs by intracerebroventricular (i.c.v.) infusion of the specific antagonist 2-amino-5-phosphopentanoate (AP5) impaired SRM acquisition in the watermaze at concentrations that also blocked dentate gyrus LTP *in vivo*[35-37]. However, given the i.c.v. route of drug administration, there followed considerable debate,

(i) as to the brain locus of these effects (hippocampal (CA and DG subfields) vs. extra-hippocampal), and (ii) whether the watermaze deficit in these animals 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 watermaze task, if they had received watermaze pre-training in a different spatial environment prior to testing with the drug (the spatial upstairs/downstairs task)[32,38]. This result suggested that hippocampal NMDARs were not after all essential for (i) forming a spatial representation of a novel environment, (ii) forming an association between a particular spatial location and the escape platform, or (iii) efficient spatial navigation through an environment.

Studies with NMDAR subunit knockout mice

Advances in genetic engineering provided an alternative approach for testing the LTP/memory hypothesis. This allowed key proteins required for either the induction or expression of LTP, such as NMDAR subunits, to be ablated and the effects on behaviour 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 adult neocortex and hippocampus are GluN2A and GluN2B.

The first study on an NMDAR knockout mouse initially appeared consistent with the LTP/memory hypothesis. This study reported that mice lacking the GluN2A subunit of the NMDAR (formerly known as the NR2A or the epsilon 1 subunit; ε1) throughout the brain were impaired on the standard watermaze task and also showed reduced hippocampal LTP[41]. However, in marked contrast to this original report, subsequent studies performed after extensive back-crossing to the C57BL/6 strain,[42] found that *GluN2A*$^{-/-}$ mice actually acquired the standard, SRM version of the watermaze task as well as their wild-type littermate controls[43]. Mice in which the C-terminal intracellular domain of the GluN2A subunit was selectively deleted (*GluN2A*$^{\Delta C/\Delta C}$ mice) also showed normal SRM. Notably, both the *GluN2A*$^{-/-}$ and *GluN2A*$^{\Delta C/\Delta C}$ mice were impaired during SWM/short-term memory tasks, suggesting an important role for the GluN2A subunit in non-associative, short-term memory processes (see BOX 2).

Hippocampus-specific GluN1 knockout mice

A crucial advance in validating the hippocampal LTP/spatial memory hypothesis appeared to have arrived with the generation of region-specific conditional knockout mice. Mice in which the *Grin1* 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* [44,45]. The SRM watermaze impairment described in these conditional *Grin1* knockout mice, along with the absence of LTP at Schaffer-collateral-CA1 synapses, was taken as confirmation that long-term, associative spatial memories are indeed encoded in the hippocampal CA1 region via an NMDAR-dependent LTP-like mechanism[45]. In fact, this result rapidly became the cornerstone of the hippocampal LTP/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 *Tg-29-1/Grin1* knockout mice demonstrated that the NMDAR depletion extends beyond the hippocampus and spreads into cortical areas, thus confounding interpretation of the watermaze impairment[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 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 *Tg-29-1*/*Grin1* knockout mice are also significantly impaired on a non-spatial version of the watermaze task. Therefore, it is not possible to attribute the spatial memory watermaze deficit in these mice specifically to NMDAR loss in the hippocampus.

A dissociation in long-term spatial reference memory

Recent generation of a novel, genetically modified mouse line has provided an alternative way to test the hippocampal LTP/spatial memory hypothesis. In this line, the GluN1 subunit is selectively deleted from dentate gyrus (DG) granule cells and dorsal CA1 pyramidal cells of adult mice, leaving NMDARs in cortex and elsewhere in the brain intact (*Grin1*$^{\Delta DGCA1}$ mice[33]). The loss of NMDARs from CA1 and DG principal cells results in the loss of LTP at CA3–CA1 synapses in these mice, and surprisingly a reduction in DG granule cell number. Nevertheless, these *Grin1*$^{\Delta DGCA1}$ mice perform perfectly well on the SRM version of the Morris watermaze task (Figure 2b). In fact on probe tests in which the platform is removed

from the pool and the mice allowed to swim freely for 60 s, *Grin1*$^{\Delta DGCA1}$ mice actually spend more time searching in the target quadrant than controls.

In marked contrast, *Grin1*$^{\Delta DGCA1}$ mice are 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 (see BOX 1; Figure 2c). Notably, mice in which the GluN1 subunit is selectively deleted just from dentate gyrus granule cells are not impaired on the SRM radial maze task[51], demonstrating that NMDARs in the CA1 subfield make an important contribution to performance on this task (see 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 watermaze experiment. *Grin1*$^{\Delta DGCA1}$ mice were trained on a spatial discrimination task with two visually identical beacons on the water surface, only one of which indicated the position of the hidden escape platform (Figure 3b). 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 perfectly capable of learning the spatial location of the platform (as measured using probe tests, during which the platform and beacons were removed from the pool; Figure 3b, *right*), they were more likely to choose the incorrect, decoy beacon and made more errors overall (Figure 3b, *left*). This deficit was primarily seen on trials during which the mice were started from close to the decoy beacon (S- trials; Figure 3c, *right*). *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 watermaze study, mice were trained to discriminate between the two visually identical beacons, depending on their allocentric spatial locations, but now all of the trials started from either of the two equidistant start positions. There was no deficit in the *Grin1*$^{\Delta DGCA1}$ mice during this acquisition phase. However, they were then subsequently impaired during probe trials starting from 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 were used (e.g. black/white striped cylinder vs. grey funnel), and with multiple start

locations, the *Grin1*$^{\Delta DGCA1}$ mice are unimpaired, even on trials starting from close to the incorrect beacon (Figure 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, perfectly capable of learning the spatial location of the platform (see also Figure 2b). Instead, the dissociation may result from the inherent ambiguity present in the task when using visually identical beacons but which 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. In 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 platform, and beacon means no platform), and so the beacon is an ambiguous cue. The mice must therefore use the spatial cues as a conditional cue or occasion setter as to whether or not 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 context fear conditioning compared to cue (e.g. tone) conditioning[53] (see [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].

Reappraising 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 DG, 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. DG lesions restricted to dorsal hippocampus have been shown to produce deficits in SWM during a matching to place task on an 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 with genetically modified mice have also supported a role for NMDARs in DG 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 behavioral effects of ablating adult neurogenesis in the dentate gyrus 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 employed in different studies[64] (but see also[65]).

However, the SRM radial maze impairment in the *Grin1*$^{\Delta DGCA1}$ mice is independent of the spatial separation between the arms of the maze (Figure 2c, *right*)[33,51]. Furthermore, the various watermaze results demonstrate that *Grin1*$^{\Delta DGCA1}$ mice can successfully discriminate between, and use the extramaze spatial cues perfectly well. 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 (i.e. all the arms have the same physical appearance), and which 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 don't run) for each arm, just as they have to select between approaching or avoiding the beacons in the spatial discrimination watermaze task. *Grin1*$^{\Delta DGCA1}$ mice are unable to "pattern" separate the "arm-food" and "arm-no food" memories (or separate between the "beacon-platform" memory and the "beacon-no platform" 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 played by hippocampal NMDARs lies in selecting between competing and conflicting memories, and between the different behavioural response choices 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 are impaired during spatial reversal testing in the watermaze 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]. On this task, animals are pre-trained as normal animals on a standard SRM version of the watermaze 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 watermaze 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 to learning an entirely new spatial layout. *Grin1*$^{\Delta DGCA1}$ mice are also impaired during spatial reversal in the watermaze (Figure 2b, *right*)[33]. The watermaze 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 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 watermaze acquisition training (Figure 2b, Transfer Test; see also[67]).

Likewise, the delayed-match-to-place (DMTP), SWM version of the watermaze 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 are impaired on this task[68], as are mice in which NMDARs have been ablated from the CA3 subfield[69]. Integral to successful performance on the DMTP task is the ability to detect and resolve the conflict between currently valid and previously valid platform locations, and to behaviorally inhibit the response to go back to previous platform locations. Thus, the deficits that occur following blockade or ablation of hippocampal NMDARs on the spatial reversal and DMTP 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, ablation of NMDARs from either DG alone or from CA3 does not impair SRM acquisition in the watermaze[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/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 with genetically modified mice which 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 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 role during acquisition of the SRM watermaze task. The *Tg29-1 Grin1* knockout mice were, after all, impaired during acquisition of the standard SRM version of the watermaze task, although they were also mildly impaired on the visible platform task[45]. Taken in combination with the absence of a watermaze impairment in our 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 across studies with conditional NMDAR GluN2B subunit knockout mice. Whereas ablation of the GluN2B subunit in both hippocampus and cortex impaired watermaze 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 clearly demonstrate that NMDARs either elsewhere in the extended hippocampal formation, such as the entorhinal cortext[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 hippocampal function

So maybe what needs to be re-considered 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 tasks, but alongside these there are numerous examples of hippocampal lesions also affecting non-spatial memory tasks[74-79]. Furthermore, there is considerable evidence that the hippocampus plays 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 role in aspects of emotionality, and in mediating the action of anti-depressant drugs[83] (but see also[84]). Hippocampal lesions also reduce anxiety in a number of different ethological, unconditioned paradigms like the elevated plus maze (EPM)[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 last decade it has become increasingly clear that the spatial memory and anxiety functions of the hippocampus are preferentially associated with its dorsal (posterior: septal pole) and ventral (anterior: temporal pole) subregions respectively (Figure 4). Although the internal circuitry of the hippocampus is remarkably regular along its septo-temporal (dorsoventral) axis, the extrinsic connectivity is very different for the dorsal and ventral subregions (posterior and anterior hippocampus respectively in the primate brain)[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 hypothalamic-pituitary-adrenal (HPA) axis.

Functionally, this is reflected in a double dissociation between the effects of selective, fibre-sparing dorsal and ventral hippocampal lesions. While dorsal lesions impair performance across a wide range of spatial memory tasks, ventral hippocampal lesions have very little, if any, effect[75,92-96]. In 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 behavior 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 the 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 organisation along the septotemporal (dorsal/ventral) 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 organisation, 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 tasks 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 inform on 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 distinct from fear, which is the response to imminent danger, and different neural circuits are involved in these different defensive or protective 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 a variety of routes. For example, there is conflict between potential unlearned outcomes in simple, ethological, unconditioned laboratory tests of anxiety, like the elevated plus maze. Such tests are based on approach/avoidance conflict, with the animal being required to choose between whether to

explore the open, exposed arms of the maze which are potentially dangerous but also potentially rewarding (approach), or stay in the safe, enclosed sections (avoidance).

Jeffrey A. Gray, and subsequently Gray and McNaughton, 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[80,81]. This involves increasing arousal levels, modulating attentional processes in order to change the salience of stimuli in the environment, and, importantly, suppressing on-going motor programs (behavioural inhibition). Furthermore, Gray suggested that it is the septo-hippocampal system that subserves these functions. Our data have re-energised 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 deficit in *Grin1*$^{\Delta DGCA1}$ mice in the spatial discrimination watermaze task on the start position of the trials (Figure 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 which have emphasised 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[124,125] and lesion studies in rodents[79,126,127], have implicated the hippocampus, and particularly the CA1 subfield, in the response to associative mismatch and conflict of this kind. For example, rats exposed to two separate audiovisual sequences (e.g. tone-constant light; click-flashing light) will learn these sequences and habituate to the cues. However, if the auditory cues preceding the visual stimuli are switched (i.e. tone-flashing light; click-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 *Grin1*$^{\Delta DGCA1}$ mice are impaired in the standard, open field watermaze 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, would be prevented by NMDAR deletion in *Grin1*$^{\Delta DGCA1}$ mice. Thus, the hippocampal comparator may play an important role 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 role for place cells? Although cells in the hippocampus are clearly 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 like the watermaze or the radial maze. Single-unit recording studies alone cannot demonstrate the causal roles of the activity they monitor. Furthermore, recent studies of hippocampal unit activity in genetically modified mouse lines suggest that the relationship between place cell/place field fidelity and spatial memory abilities on behavioural tasks like the watermaze and radial maze is not straightforward. For example, Resnik et al.,[128] recently reported that place cells recorded in the dorsal CA1 region of mice lacking GluA1-containing AMPARs throughout the brain are substantially disrupted. 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 watermaze and radial maze tasks proceeds unimpaired in mice lacking GluA1 (Figure 1b,c)[20,129,130]. In line with a hypothesis that the hippocampus acquires and encodes spatial information, it was 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 was also 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 it 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] (Figure 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 restricted to GABAergic interneurons routinely exhibit a behavioral phenotype of impaired SWM/short-term memory but normal SRM (see BOX 4). Despite this, differences between these mutants at the cellular and network level are quite remarkable. For instance, *Grin1*$^{PV-/-}$ mice, which lack NMDARs in parvalbumin-positive GABAergic neurons throughout the brain, and *Cx36*$^{-/-}$ mice, which do not express connexin36, exhibit both reduced spatial and temporal coding[131,132]. However, the deficit in mice lacking GluA4 subunit-containing AMPARs, specifically in hippocampal parvalbumin-positive interneurons, is reflected solely in impaired temporal coding, leaving spatial coding 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 appear essential for long-term SRM.

Therefore, further experiments are required to understand fully 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 entorhinal cortex, for 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 in spatial tasks but also in non-spatial memory tasks, and to anxiety.

Conclusions

Recent studies in *Grin1*$^{\Delta DGCA1}$ mice challenge head-on 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/memory hypothesis that is wrong but rather that it is the role of the hippocampus that needs to be re-examined. Extra-hippocampal NMDARs play an important role in spatial learning, 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 perform a critical role within a comparator/behavioural inhibition system for detecting and resolving conflict or uncertainty, such as might occur between ambiguous or overlapping memories, or between competing behavioural goals (e.g. during anxiety tests). It has been suggested previously that the hippocampus may play 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 emphasised 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. In contrast, semanticised 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 which also explains its role in anxiety[81].

BOX 1: Behavioral tests of long-term spatial memory in rodents

Allocentric spatial learning and memory is assessed in rodents using a wide variety of tasks, all of which are impaired by hippocampal lesions. The large number and variety of tasks employed makes a detailed description of all of these paradigms beyond the scope of this review. Below are descriptions of the two key tasks most widely used to assess associative, long-term SRM in rodents.

Open field watermaze: In this task rodents have to locate a hidden, escape platform 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 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 (e.g. body-turn) to find the platform. Latencies and pathlengths 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 allowed to swim freely for 60 sec. Animals with good spatial knowledge of the platform location will spend most time searching in the appropriate region of the pool (the Goal (G) or target quadrant).

Radial arm maze: SRM and 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. By rewarding only certain arms but always rewarding the same arms, SRM can be assessed. 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 assessed simultaneously. 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 (i.e. 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.

BOX 2: GluA1 and short-term memory

The GluA1 subunit is thought to play an important role in aspects of AMPAR trafficking[135,136] and in mechanisms underlying synaptic plasticity, particularly short-term forms of plasticity[130,137-139]. GluA1 is also important for 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 GluA1 AMPAR subunit) have an impaired ability to represent familiarity based on 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 (e.g. 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].

BOX 3: Mice lacking NMDARs in the dentate gyrus

Genetically modified mice lacking the GluN1 subunit, and hence NMDARs, specifically in dentate gyrus granule cells have also been generated (*GluN1*$^{\Delta DG}$ 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 (Yasuhito Watanabe, PHS & HM, unpublished). Crucially, the behavioural phenotype in these *GluN1*$^{\Delta DG}$ mice is much reduced from that seen in the *Grin1*$^{\Delta DGCA1}$ mice. In particular, they are not impaired at acquiring the spatial reference memory radial maze task[51] (which is dramatically impaired in the *Grin1*$^{\Delta DGCA1}$ mice; see Figure 2C). Importantly, this therefore demonstrates that the ablation of NMDARs in CA1 must play at least some role in the behavioral deficit in the *Grin1*$^{\Delta DGCA1}$ mice. Notably, *GluN1*$^{\Delta DG}$ mice are impaired on the spatial working memory component of the radial maze task.

BOX 4: GABAergic interneurons and spatial memory

Studies with genetically modified mice have highlighted the crucial role of GABAergic interneurons for specific aspects of spatial information processing at the network and behavioral level. Selective AMPAR 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 SWM performance but are not required for SRM. In fact, the SWM deficit in *Gria1*$^{PV-/-}$ mice is almost as pronounced as that reported for mice with global GluA1 deletion. Ablation of the GluN1 subunit of the NMDAR from parvalbumin-positive interneurons of the forebrain is also associated with a SWM deficit, again leaving SRM intact[131]. Conceptually, maybe even more interestingly, ablation of gap junction coupling between interneurons recapitulates this same behavioral phenotype[132]. Thus, interfering with interneuron activity ensures dissociation between SWM and SRM. This hypothesis has been further strengthened using cell type 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 to 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 behavioral deficit is less surprising if one considers that GABAergic interneurons are the major players ensuring a range of distinct oscillatory activities that are considered 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 performance.

GLOSSARY OF TERMS

AP5 – AP5 is a competitive antagonist at the NMDA glutamate receptor subtype. The drug competes with glutamate to bind to the NMDAR and thus reduces the activity of these receptors.

Boundary vector cells – Boundary vector cells (BVCs) were first predicted to exist by computational models, and then subsequently discovered in entorhinal cortex[16,17] and subiculum[18]. BVC firing depends solely on the animals location relative to environmental boundaries and is independent of the animals heading direction.

Dissociation – When an experimental manipulation (e.g. a lesion, genetic modification or drug treatment) affects performance on one behavioral task but not another, it is said that there is a dissociation between the two tasks. This is taken to suggest that different neural substrates may underlie the two behaviors.

Double dissociation – When a given experimental manipulation affects task A but not task B, whereas a second manipulation affects task B but is without effect on task A, then this is described as a double dissociation. A double dissociation is evidence that these behaviours must be supported by different neural substrates.

Grid cells – Unlike hippocampal place cells, which fire in only one part of a given environment, grid cells fire at several regularly spaced locations, with marked inhibition of firing outside of these locations[13]. Thus a map of peak firing rates resembles a hexagonal lattice. It has been suggested that grid cells could provide the distance metric by which space is coded. Grid cells have been found in layer 2/3 of the medial entorhinal cortex.

Head direction cells – Head-direction (HD) cells are 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[15]. They signal a single preferred head direction, irrespective of body-orientation or current position; whether the animal is moving or stationary. HD cells appear to be controlled, in part, by distal sensory input and, like place cells, re-align to the rotation of salient environmental cues. They are also, in part, driven by

interoceptive cues (e.g. vestibular and/or proprioceptive cues). HD cells are most commonly found in anterior thalamus and dorsal presubiculum.

Place cells – Place cells are 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[7]. Thus, the place cell is typically silent as the animal moves around the environment until it enters the place field. Place cells are usually recorded in the hippocampus proper, but they are also present in other areas of the hippocampal formation (e.g. entorhinal cortex, subiculum, presubiculum and parasubiculum).

Spatial reference memory – Spatial reference memory (SRM) is the ability to learn a consistent, fixed response to a spatial stimulus, reflecting a constant association between that spatial location and an outcome[151]. 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 – Spatial working memory (SWM) requires 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[151,152]. This is the basis of foraging behaviour (e.g. remembering where you have just been so that you can adopt an efficient search strategy).

FIGURES

Figure 1: GluA1 is required for short-term, but not long-term spatial memory. a. Mice lacking the GluA1 AMPAR subunit (*Gria1*$^{-/-}$ mice; light grey) and wild-type controls (*Gria1*$^{+/+}$ mice; dark grey) were compared on tests of spatial memory. **b.** GluA1 is not required for spatial reference memory (SRM) in the watermaze[129,130]. *Gria1*$^{-/-}$ mice and controls exhibit similar latencies to find a hidden escape platform in a fixed spatial location (shown as a dotted circle, "G") during acquisition training. They also show an equivalent preference for the goal (G) or target quadrant (i.e. the quadrant that normally contains the platform) during a Transfer (probe) test (TT) conducted at the end of acquisition training, during which the platform is removed from the pool and the mice allowed to swim freely for 60 s (*see inset,* where each bar on the histogram represents time in a quadrant of the pool). **c.** GluA1 is required for spatial working memory (SWM) performance (which depends on short-term memory) but not for SRM (which depends on long-term memory) on the radial maze. Mice are trained to discriminate between which arms of the radial maze contain a food reward (+ arms) and which arms are never rewarded (- arms). An entry into a never rewarded arm constitutes a SRM error. *Gria1*$^{-/-}$ mice can exhibit faster acquisition of the SRM component of the radial maze task than wild-type controls, making less SRM errors as training proceeds[20]. In contrast, *Gria1*$^{-/-}$ mice repeatedly re-enter arms that they have already visited on that trial and which are now no longer rewarded. This constitutes a SWM error. *Gria1*$^{-/-}$ mice make more SWM errors than wild-types[20,140] (*see inset*). **d, e.** The absence of short-term spatial memory in mice lacking GluA1 can result in the facilitation of long-term spatial memory in these animals. *Gria1*$^{-/-}$ mice show impaired short-term spatial memory, but in contrast, they actually demonstrate enhanced long-term spatial memory, measured using **d,** 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). 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 = (Novel/Novel+Other)), shows that *Gria1*$^{-/-}$ mice exhibit impaired short-term spatial memory, but enhanced long-term spatial memory. Adapted from[10]. Broken line = chance performance.

Figure 2. Impaired spatial reference memory on the radial maze but normal spatial reference memory in the open field watermaze in *Grin1*$^{\Delta DGCA1}$ mice.

a. Hippocampal NMDAR expression in *Grin1*$^{\Delta DGCA1}$ and control mice. **b.** Control (grey) and *Grin1*$^{\Delta DGCA1}$ mice (blue) acquired the spatial reference memory (SRM) version of the watermaze at a similar rate. They exhibited similar pathlengths to find a hidden escape platform in a fixed spatial location (shown as a dotted circle, "G") during acquisition training. *Grin1*$^{\Delta DGCA1}$ mice actually spent more time searching in the goal (G) quadrant (i.e. 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 allowed to swim freely for 60 s (*see inset,* where each bar on the histogram represents time in a quadrant of the pool). However, *Grin1*$^{\Delta DGCA1}$ mice were impaired when the platform was then moved to the diametrically opposite position in the watermaze (Reversal). **c.** *Grin1*$^{\Delta DGCA1}$ mice (blue) were also impaired relative to Controls (grey) at acquiring the SRM component of the radial maze. Mice are trained to discriminate between which arms of the radial maze contain a food reward (+ arms) and which arms are 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. An entry into a never rewarded arm constitutes a SRM error. *Grin1*$^{\Delta DGCA1}$ mice made more SRM errors than Controls during Acquisition. Regarding 'Error types', the impairment in *Grin1*$^{\Delta DGCA1}$ mice is not dependent on the spatial separation between the arms of the maze (errors into adjacent (divided by 2) or single non-rewarded arms)[33,51]. *Grin1*$^{\Delta DGCA1}$ mice (blue bars) made more SRM errors than controls (grey bars) into both single and adjacent non-rewarded arms.

Figure 3. Impaired spatial discrimination but normal non-spatial discrimination in the watermaze in the *Grin1*$^{\Delta DGCA1}$ mice.

Control (grey) and *Grin1*$^{\Delta DGCA1}$ mice (blue) were compared on both a spatial discrimination and a non-spatial discrimination beacon task in the Morris watermaze[33]. **a.** Hippocampal NMDAR expression in *Grin1*$^{\Delta DGCA1}$ and control mice. **b.** On the spatial discrimination task there were two visually identical beacons (grey spheres) sitting on the water surface, only one of which indicated the position of the fixed location, hidden escape platform (shown as a dotted circle). The correct and decoy beacons were differentiated solely by their allocentric spatial locations relative to the extramaze room cues. *Grin1*$^{\Delta DGCA1}$ mice (blue) were much more likely to choose the wrong beacon than Controls (grey), and made more errors during Acquisition. This was despite showing an equivalent, strong preference for the goal (G)

quadrant (i.e. the quadrant that normally contains the platform) during a Transfer Test (TT) conducted at the end of training. Each bar on the histogram represents time in a quadrant of the pool. **c.** During acquisition of the task, trials started at the edge of the pool, pseudorandomly either from a point close to the correct beacon (S+ Trials), or from a point close to the incorrect, decoy beacon (S- trials), or from a point equidistant between the two beacons (Equid. Trials). The deficit in *Grin1*$^{\Delta DGCA1}$ reflected lower performance (% Correct choices) on trials that were started from close to the wrong/decoy beacon (S- Trials). Broken line = chance performance. **d.** On the non-spatial, visual discrimination task the mice were required to choose between two visually distinct beacons (grey funnel vs. black/white cylinder) whose spatial locations moved randomly from trial to trial. The platform (shown as a dotted circle) was always associated with one particular beacon (e.g. the black/white cylinder) for a given animal. Controls (grey) and *Grin1*$^{\Delta DGCA1}$ mice (blue) made a similar number of choice errors on the non-spatial version of the task. **e**. During acquisition of the non-spatial task, trials also started at the edge of the pool, pseudorandomly either from a point close to the correct beacon (S+ Trials), or from a point close to the incorrect, decoy beacon (S- trials), or from a point equidistant between the two beacons (Equid. Trials). There was no difference in choice accuracy between *Grin1*$^{\Delta DGCA1}$ and Controls from any of the start positions (% Correct choices). Broken line = chance performance.

Figure 4. Distinct contributions of dorsal and ventral hippocampus to behavior. Sub-region specific, cytotoxic lesions have fractionated the hippocampus in terms of their behavioral effects. The dorsal hippocampus (posterior hippocampus in primates: septal pole) subserves the spatial memory functions of the hippocampus (e.g. in the watermaze and radial maze), whereas the ventral hippocampus (anterior hippocampus in primates: temporal pole) underlies the anxiolytic effects of hippocampal lesions (e.g. on the elevated plus maze).

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Figure 1

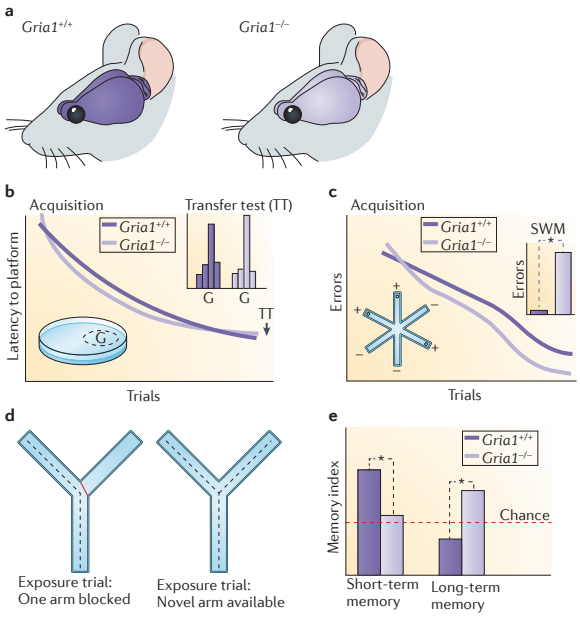

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Figure 2

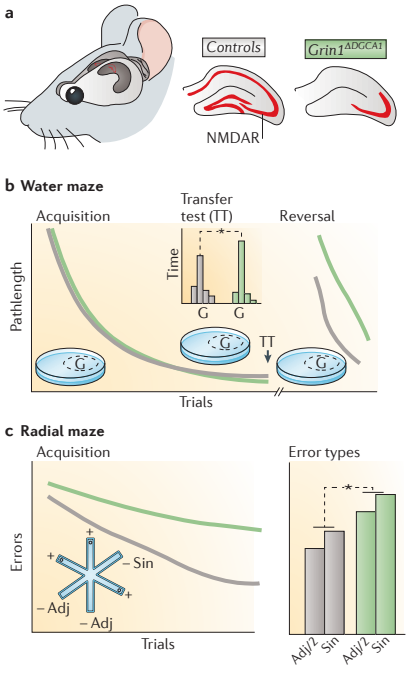

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Figure 3

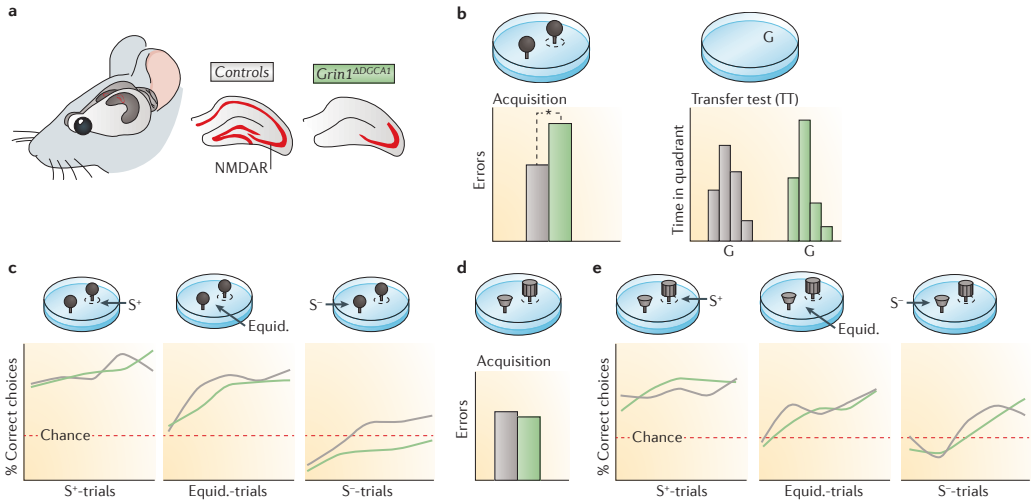

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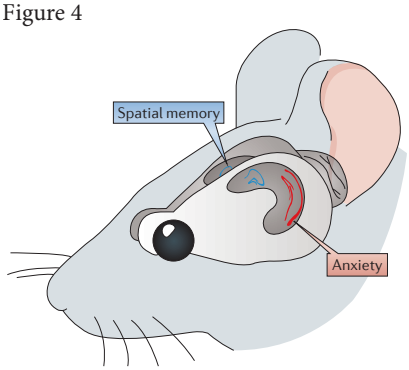
Figure 4



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