Review

The synaptic plasticity and memory hypothesis: encoding, storage and persistence

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The synaptic plasticity and memory hypothesis asserts that activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation and is both necessary and sufficient for the encoding and trace storage of the type of memory mediated by the brain area in which it is observed. Criteria for establishing the necessity and sufficiency of such plasticity in mediating trace storage have been identified and are here reviewed in relation to new work using some of the diverse techniques of contemporary neuroscience. Evidence derived using optical imaging, molecular-genetic and optogenetic techniques in conjunction with appropriate behavioural analyses continues to offer support for the idea that changing the strength of connections between neurons is one of the major mechanisms by which engrams are stored in the brain.

1. Introduction

The idea that changes in the efficacy of synapses within diverse neural circuits could mediate the storage of information acquired during learning has a long history. Theoretical hypotheses about the growth of neuronal connections in the brain and the circumstances in which such growth might take place date back to Ramón y Cajal [1] and, in the mid-twentieth century, to Hebb [2] and Konorski [3]. The first experimental evidence emerged from studies of habituation and sensitization in the marine mollusc *Aplysia* [4,5]. The discovery of long-term potentiation (LTP) [6] acted as a further stimulus to the concept, not least because LTP was first discovered in an area of the brain—the hippocampal formation—that had been implicated in memory from clinical observations of amnesia [7]. Indeed, the last sentence of Bliss & Lömo's paper raises the question. Noting the possibility that the time-scale of LTP was long enough to be potentially useful for information storage, they go on to conclude in characteristically quizzical fashion:

> whether or not the intact animal makes use in real life of a property which has been revealed by synchronous, repetitive volleys to a population of fibres the normal rate and pattern of activity along which are unknown, is another matter. [6, p. 355].

In our quest for understanding 'mechanisms' in neuroscience, a focus in research on activity-dependent synaptic plasticity such as LTP and long-term depression (LTD) has been on identifying the causal steps that occur at individual synapses mediating lasting changes in synaptic efficacy in terms of changes in presynaptic transmitter release, alterations in postsynaptic glutamatergic receptors, the action of neuromodulatory transmitters, the signal transduction pathways activated, gene activation and synthesis of new proteins. A contemporary focus is on the endo- and exocytosis of specific sub-types of glutamate receptors, and alterations in the scaffolding molecules that make up the pre- and postsynaptic elements of neuronal connectivity [8]. Recent reviews of the persistence of LTP/LTD collectively point to the importance of translational control of dendritic mRNAs, and that spine dynamics may be remarkably fast to be in register with the relatively immediate functional changes [9–11]. Accompanying papers in this issue discuss similar themes.

However, in our view, no less important is Bliss & Lömo's now 40-year-old question—do animals actually make use of this capacity for change and, if so, how? This systems-level question was initially approached in terms of seeking correlations between learning and synaptic potentiation [12], but the diverse techniques of contemporary neuroscience offer new tools for securing a definitive and causal answer [13,14], and addressing whether such understanding could be a route towards more effective cognition [15]. Here, we review progress in identifying whether and how synaptic plasticity may mediate distinct aspects of learning and memory with focus on the hippocampus, beginning with the generic hypothesis.

2. The synaptic plasticity and memory hypothesis

The synaptic plasticity and memory (SPM) hypothesis is not identified with any one individual scientist, it being an idea that has come forward in various guises over the years (see [16] for review). At its heart is the notion that the memory of prior experience is mediated by the reactivation of 'traces' or 'engrams' whose basis involves alterations, possibly bidirectional alterations, in synaptic efficacy. The intellectual debt to Hebb, in particular, is very clear but the concept of 'memory of prior experience' has to be unpacked with respect to the distinct ways in which it can be interpreted. The most everyday sense of memory is that of an event happening to someone, it somehow being recorded in their brain, and then this person later bringing to mind some representation of that same event. One can think of this loosely as 'real' memory in the everyday 'folk-psychology' sense of the term. However, prior experience may also induce changes in the nervous system, possibly mediated by synaptic plasticity, that in no sense allow recall of the prior experience that occurred. A runner training for a marathon will gradually build up muscle mass and all manner of changes in his or her body that reflect the experience of training. However, changes in muscle mass in no sense 'represent' the actual events that constitute that training, even though they are triggered by it. These two examples of putative 'memory' can be thought of as qualitatively distinct ways in which experience drives plasticity, or alternatively, as two ends of a continuum. Huebener & Bonhoeffer [17] take a 'continuum' point of view, suggesting that study of the neural mechanisms of ocular dominance or orientation-sensitive plasticity could be a valid route to discovering the neural mechanisms of memory. The fine-tuning of cortical connections in the visual system during the sensitive period of early development is now known to involve bidirectional changes in synaptic efficacy mediated by LTP-like and LTD-like mechanisms, and various tantalizing phenomena potentially relevant to memory have recently been discovered such as 'savings' with respect to future plasticity after incomplete experiences during infancy. Specifically, Hofer *et al.* [18] have demonstrated successful adult cortical plasticity in mice that had a period of eye closure during the sensitive period that was then terminated early on. This phenomenon is reminiscent of the 'savings' that can be seen in learning a second language if a person has been exposed, at least for a period, to that language early in life. Huebener and Bonhoeffer's view is that drawing a sharp categorical boundary between 'real' memory and the diverse array of experience-dependent changes that occur in the nervous system throughout life is both unnecessary and misleading.

However, while accepting the force of this argument, a problem is that while the underlying neural mechanisms of plasticity at glutamatergic synapses may be very similar for changes right across this continuum, the function(s) that activity-dependent synaptic plasticity serves will, in our view, depend critically on the neural circuit in which that plasticity is embedded in a non-monotonic manner. Let us contrast two cases. Pre-synaptic facilitation at the sensory to motor neuron synapse of the abdominal ganglion of *Aplysia* is thought to realize an increase in synaptic throughput that mediates a behavioural facilitation of responsiveness. A stimulus to the siphon then gives rise to a larger and longer withdrawal of the gill and siphon reflex. Conversely, habituation is associated with a decrease in transmitter release measured using quantal analysis [5]. In these cases, there is an elegant isomorphism between the physiological change and the behavioural change that has been likened to a 'cellular alphabet of learning' [19]. A similar principle may also apply to fear conditioning mediated by the amygdala of mammals in which an initially neutral stimulus can, through synaptic potentiation mediated by changes in post-synaptic receptor expression [20], give rise to graded evocation of fear through associative conditioning with a painful or biologically dangerous stimulus (e.g. a predator). The amygdala's efferent connections trigger the various expressions of that fear via downstream connections to the autonomic nervous system [14]. Isomorphism may be a common characteristic of learned reflex systems.

What is less well appreciated is, however, that other neural circuits of memory do *not* operate on an isomorphism principle. Rather, synaptic potentiation and depression sculpt the possibility of associations between stimuli such that learning, rather than giving rise to larger or smaller responses, enables one stimulus representation to evoke the memory representation of another. This is qualitatively different. For example, a key characteristic of episodic-like memory is what has been called the 'automatic recording of experience' [21] whereby the memory of an event is automatically associated with the context in which it happens. Biologically significant events such as reward and punishment are not necessary for making such associations; nor need they enter into them in the conventional sense of Pavlovian conditioning between a conditional stimulus (CS) and a biologically significant unconditioned stimulus (US). Instead, the co-occurrence of events and contexts enables, in the distributed associative machinery of the hippocampal formation operating on Hebb-like principles, an association that ties these two entities together. That is, if you remember an event you will automatically remember the context where it happened. Realizing this kind of association requires distributed temporo-spatial representations of events and contexts that can be discriminated (pattern separation) and sometimes generalized (pattern completion), with multiple events and contexts overlaid in a distributed manner within a common neural circuit [22]. Hebbian synaptic plasticity, possibly coupled to associative synaptic depression, within a neural circuitry that enables distributed associative memory through the pattern of excitatory and inhibitory interconnections will realize this function—albeit subject to the myriad of inhibitory feed-forward and feedback connections that regulate excitability in different compartments of the dendritic tree [23]. The Huebener–Bonhoeffer

continuum principle, with its focus on mechanism at the level of *individual* synapses, does not yet provide an effective framework for thinking about these systems-level issues. In fact, at a systems-level, we are a long way from understanding the detailed manner in which information is represented in temporo-spatial codes, how the interplay of excitatory and inhibitory activation enables encoding and later retrieval, and even the distinct and sometimes sparse representational codes of different sub-regions of the hippocampal formation [24]. However, computational neuroscience techniques are proving invaluable in tackling these issues and a systems approach is essential if the representational issues are to be addressed mechanistically.

Two last points to make about the generic SPM hypothesis concern plasticity itself and new techniques. Research over the 40 years since LTP was discovered has revealed a family of different forms of activity-dependent synaptic plasticity. In addition to NMDA receptor-dependent LTP and LTD, there are forms of synaptic potentiation and depression that are NMDA receptor-independent. Homeostatic plasticity has been discovered and it may play both a normalizing and protective role in neural circuits that might otherwise be risk at seizure through potentiation of too high a proportion of neural afferents [25]. Spike-timing-dependent plasticity [26,27] has been implicated in the learning and expression of, for example, remembered sequences [28]. Second, contemporary neuroscience is characterized by an array of novel technologies including new molecular-genetic technologies, optical imaging in living animals and optogenetic manipulations of individual neurons [29–34] as well as new behavioural paradigms [35–37]. Their use, illustrated below, is offering the opportunity to secure more definitive answers to the validity of the SPM hypothesis.

To conclude, this hypothesis can be stated, in its most general form as follows:

> activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the encoding and trace storage of the type of memory mediated by the brain area in which that plasticity is observed. [16, p. 650]

This definition is intended to be both inclusive and sufficiently precise for the hypothesis to be falsifiable. We turn now to four critical tests of the hypothesis that have been examined in numerous studies over the past 25 years.

3. Criteria for assessing the synaptic plasticity and memory hypothesis

Martin *et al.* [16] identified four distinct criteria of assessment and corresponding tests of the SPM hypothesis. The first they called *detectability* whereby if learning involves activity-dependent synaptic plasticity, it should be possible to detect changes in synaptic efficacy following learning. This is one aspect of a 'sufficiency' criterion—that synaptic change occurs during learning—though it falls short of establishing that such a change is actually sufficient. Second, they argued that if some treatment (pharmacological, physiological and molecular-genetic) were to be given *prior* to learning, the rate of learning should be blocked, enhanced or otherwise altered in a predictable manner if the treatment in question were to alter the induction or expression of synaptic plasticity. They called this the *anterograde alteration* criterion, a component of

'necessity'. Third, if learning were to occur and then, *after* learning, certain retrograde manipulations were made that might affect the expression of earlier changes in synaptic weights, the ability of the neural circuit to reconstruct the appropriate representational pattern should be affected. The experimental subject might then behave as if it had retrieved different information from that which had been learned. This is the *retrograde alteration* criterion—a second component of necessity. Last, if memory resides in specific distributed patterns of altered synaptic weights, the artificial creation of such a pattern should result in the creation of a 'false memory' for an event that did not happen or some aspect of knowledge or skill that had not been taught or trained. This *mimicry* criterion, the second component of sufficiency and essentially the engineering criterion, is arguably the most demanding.
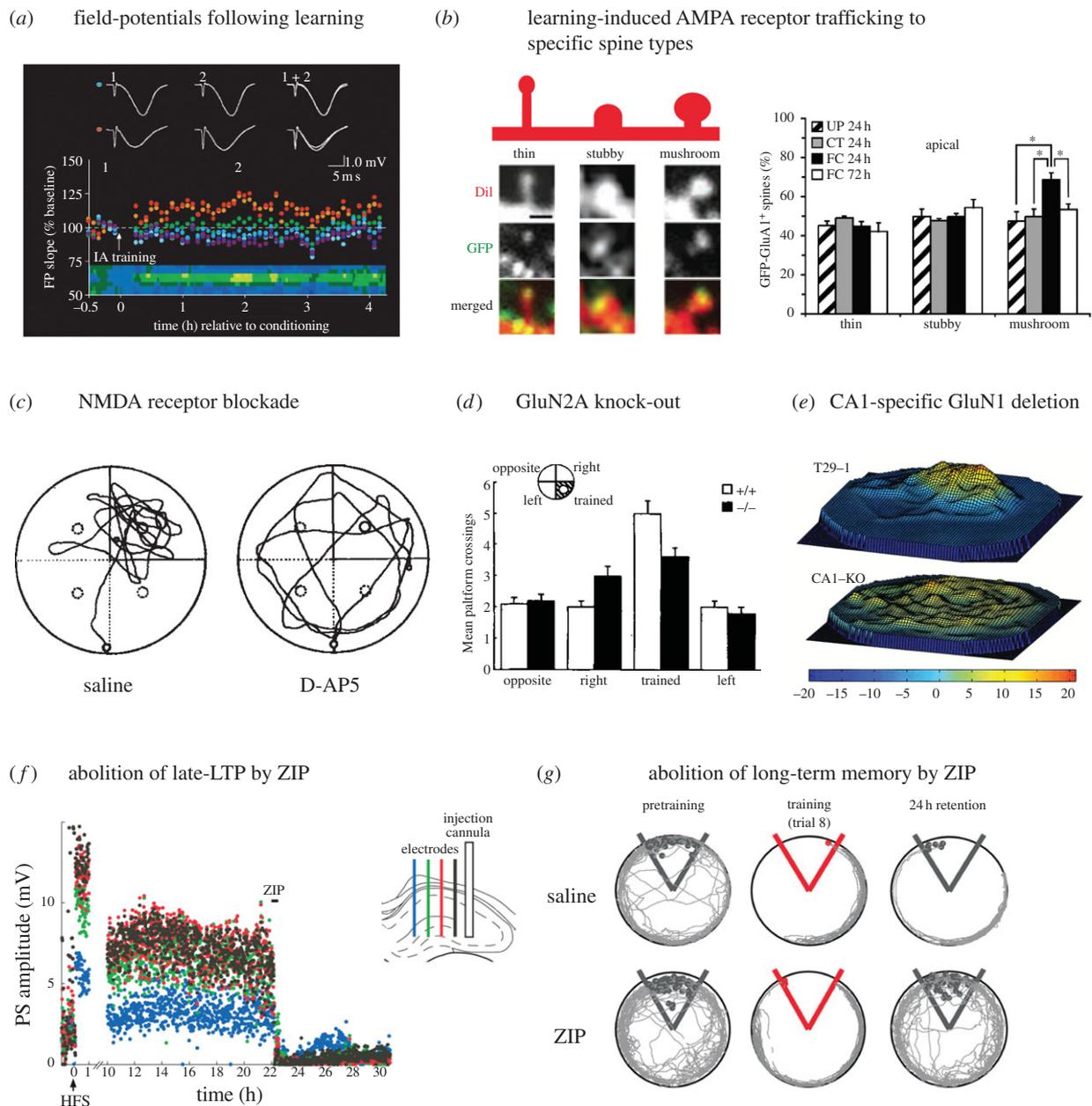
(a) Detectability

There is now strong evidence that learning can be associated with the induction of changes in synaptic weights in apparently relevant neural circuits. This is the essence of the 'detectability' criterion—with critical issues arising over what constitute relevant neural circuits for any particular instance of learning (see [38] for a detailed discussion).

The earliest attempts to detect changes in synaptic weight in association with specific experiences revealed changes in synaptic strength and the magnitude of population spikes in the hippocampal formation in association with exposure of animals, normally in isolation, to a complex social living environment [39]. It later transpired that these may, at least in part, be associated with alterations in brain temperature rather than exploration-associated changes in synaptic weights [40]. A later study, with suitable calibration for temperature, did reveal transitory changes in excitatory postsynaptic potentials (EPSPs) associated with novelty exposure, but these rapidly decayed to baseline [41].

Bear's group reconsidered the issue of changes in the hippocampus associated with learning using an inhibitory avoidance paradigm and the use of multiple recording electrodes [42]. The supposition was that a system with significant storage capacity would not be expected to show global changes across a high proportion of neurons when just a single task is learned. In keeping with this intuition, stable increases in synaptic weights were seen at some recording sites but not others (figure 1a). Subsequent induction of LTP was impaired only at the recording sites where potentiation was observed following learning. In addition, alterations in AMPA receptor phosphorylation and trafficking akin to those observed after LTP were seen in a biochemical assay. Learning-induced enhancement in synaptic strength within the hippocampus has since been observed electrophysiologically in several other tasks that engage the hippocampus, including trace eyeblink conditioning [49] and novel object recognition [50]. In the light of Whitlock *et al.*'s [42] results, it is nonetheless surprising that these later studies did not require use of multiple electrode arrays.

While detection of learning-induced synaptic potentiation through recording of electrically evoked field potentials in behaving animals provides a relatively unambiguous tool for validating the detectability criterion, it is conceivable that most learning-induced changes in synaptic strength are sparsely distributed and therefore hard to detect with field recordings. Additionally, synaptic and/or homeostatic depression may occur concomitantly in a spatially overlapping

Figure 1. Illustrative findings relevant to the established criteria for assessing the SPM hypothesis. (*a,b*) Detectability. Field-potentials are increased on some but not all electrodes of a multi-electrode array in area CA1 following inhibitory avoidance learning (Adapted with permission from Whitlock *et al*. [42] © AAAS) (*a*). AMPA receptor trafficking detected optically using a GFP label in association with learning, with GluA1 targeted specifically at mature, mushroom-shaped spines (Adapted with permission from Matsuo *et al*. [43] © AAAS) (*b*). (*c* – *e*) Anterograde alterations. Pharmacological blockade of NMDA receptors in rats with chronic infusion of D-AP5 impairs spatial learning (Adapted with permission from Morris *et al*. [44]) (*c*). Genetic knock-out of GluN2A in mice also impairs spatial learning in the watermaze (Adapted with permission from Sakimura *et al*. [45] © Macmillan Publishers Ltd) (*d*). CA1 pyramidal cell-specific knockout of GluN1 in mice also impairs selective searching in the watermaze (Adapted with permission from Tsien *et al*. [46,47] © Elsevier) (*e*). (*f,g*) Retrograde alterations. Successful abolition by ZIP of long-lasting LTP 22 h after its initial induction (*f*). Corresponding abolition of long-term place-memory on a rotating platform by ZIP (Adapted with permission from Pastalkova *et al*. [48] © AAAS) (*g*).

set of synapses, further reducing the possibility of observing a net enhancement of the evoked field response. Therefore, the use of various molecular and structural hallmarks normally associated with LTP as markers for learning-induced potentiation is a more robust way of determining whether synaptic potentiation has taken place.

AMPA receptor insertion into the postsynaptic membrane is a hallmark of NMDA receptor-dependent synaptic potentiation [51,52]. Several studies used modified AMPA receptors to monitor AMPA receptor trafficking in the hippocampus after a learning session. In a clever set of experiments, Matsuo *et al*. [43] fused GluR1 (GluA1) subunit of AMPA receptors to green fluorescent protein (GFP). Synthesis of those

receptors was regulated using a tetracycline-controlled transcriptional activation system and was also dependent on neural activity (via an immediate early gene (IEG) c-Fos promoter). The results showed a significant increase in GFP-positive spines on CA1 pyramidal neurons after contextual fear conditioning as well as after exposure to the context or footshock alone (figure 1*b*). Critically, when spines were sorted according to their type, contextual learning resulted in a relative increase in GFP-positive mushroom spines, when compared to the two control conditions. This provides strong evidence that learning results in enhanced AMPA receptor trafficking at mature, stable synapses in the hippocampus (for review of the role of mushroom-type spines in memory, see [53]). Similarly,

Mitsushima *et al.* [54] used 'electrophysiologically tagged' AMPA receptors [55] to monitor synaptic AMPA receptor delivery in CA1 pyramidal cells. Incorporation of these receptors into functional synapses could later be detected in brain slices via intracellular recordings through detection of an increased level of inward rectification. The authors have found significant increase in insertion of GluA1-containing AMPA receptors into functional synapses following inhibitory avoidance learning—a phenomenon consistent with enhancement of synaptic strength. In the light of an estimate of the number of amygdala neurons required for learned fear expression [20], the distributed nature of hippocampal circuitry suggests that these changes in rectification may also have been expressed in a subset of neurons.

(b) Anterograde alterations

Fulfilling the detectability criterion has been important, but it remains a correlation and there is no obvious way of establishing a causal link between the physiological and behavioural changes. The logic of the 'anterograde alteration' approach is to make some prescribed manipulation that is known to affect the induction or expression of synaptic plasticity and see whether doing so affects learning or memory, or vice versa.

This approach began to be influential following pharmacological studies which showed that blocking NMDA receptors—in the forebrain or locally in specific brain circuits—impaired spatial learning in a watermaze (figure 1*c*, [44]). This work was followed up by a range of dose–response, neurochemical and other behavioural protocols that collectively established that the dose–response profile of the extracellular concentration of D-AP5 with respect to impairment of learning exactly matched that for blockade of the induction of LTP, and that impairments of olfactory and spatial learning, and fear-conditioning, all followed intracerebral infusions of NMDA receptor antagonists [56,57]. Pharmacological studies have the advantage that it is relatively easy to develop a protocol that can contrast initial learning with later memory retrieval—and this established that NMDA receptor-dependent plasticity is generally required at the initial induction of a new memory, but neither for storage nor later retrieval [58–61].

Occlusion is a useful analytical design in biomedical science and has recently been deployed to examine whether prior spatial learning in a watermaze can occlude the subsequent induction of LTP. This is not generally observed with the strong high-frequency tetanization protocols often used to investigate LTP itself, but Habib *et al.* [62] have shown that it can occlude the induction of LTP in area CA1 following brief trains of low-frequency stimulation and does so in a time-dependent manner. Conversely, strong tetanization of the perforant path using multiple stimulation sites at the level of the angular bundle can saturate LTP in the dentate gyrus (DG) and occlude subsequent spatial learning [63].

One series of experiments has investigated the differential impact of NMDA receptor blockade on first versus second learning of a related task, revealing the initially surprising result that the learning of a second similar task may sometimes proceed normally in the presence of D-AP5 [64,65]. Such a finding represented a challenge to the supposition that NMDA receptor-dependent synaptic plasticity is always necessary for learning. The reasons that this sparing occurs have not been completely worked out, but are likely to reflect the combination of two major factors. The first is that any given learning task generally consists of a number of components (declarative and procedural) and that some of these generalize from one task to another—resulting in substantial 'savings' in learning the second task. However, careful task design can lead to protocols that, irrespective of how many times new learning takes place, sensitivity to NMDA receptor blockade is retained. In the case of hippocampus-dependent learning, these are episodic-like memory tasks such as delayed matching-to-place [59] in which the animals are trained and tested repeatedly using a within-subjects design. The second issue is that drug diffusion through a brain area is often incomplete such that sub-areas of a given circuit which are less affected by the drug may be used for second learning that are not used for the first [66]. If pharmacological studies have the advantage of 'reversibility', they have the major difficulty that it is extremely difficult to maintain drug concentrations at a steady-state over time or to ensure effective distribution of a drug within a brain area or network without affecting another ostensibly independent region [67].

Molecular-genetic studies, by contrast, enable a specific molecule to be knocked out. In second and third generation transgenic animals, this is done in a region-, cell- and even temporal-specific manner. In the early 1990s, a new technology for investigating the role of synaptic plasticity in learning and memory emerged from this approach and, specifically, via gene 'knockout' studies. The possibility of knocking out the NMDA receptor was naturally considered, but it was soon shown that a standard homologous recombination knockout of NR1 subunit (GluN1) displayed abnormal development (e.g. in barrel cortex) and died soon after birth [68]. The first successful NMDA receptor knockout study related to learning was conducted by Mishina's group [45], who showed that deletion of NR2A (GluN2A) affected learning in the watermaze (figure 1*d*) much as Morris's group had shown earlier with D-AP5 [44] (but see [69] for an apparent failure to replicate). However, the big step forward was the importation into neuroscience of Cre-Lox technology by Tonegawa's group in 1996 [46].

A series of ingenious studies using specific lines of mice showed, first, that it was possible to knock out the GluN1 subunit of the NMDA receptor specifically in area CA1 of the hippocampus by cross-breeding a line of mice expressing Cre downstream of the αCaMKII promoter with a separate line in which GluN1 coding sequence was flanked by LoxP sites [47]. These mice display abnormal place fields in CA1 [70] and are impaired in learning the watermaze [47] (figure 1*e*). A later study confirmed that the GluN1 knockout was relatively restricted to CA1 and subiculum, but presented evidence that it may be more widespread after two months of age [71]. Using a kainate receptor (GluK4) promoter rather than αCaMKII, this group has gone on to use this same molecular-genetic approach to dissect differential functions of NMDA receptors in distinct parts of hippocampal circuitry. For example, one study provided evidence that NMDA receptors within area CA3 were essential at memory encoding to enable pattern completion at the time of memory retrieval in a watermaze surrounding by specific sets of cues and another for what is sometimes called 'one-shot' learning [72,73]. This approach to using gene-targeting was recently extended with another promoter to include a selective deficit in pattern separation when GluN1 is deleted in the DG [74].

Another group led by Seeburg and Sakmann, with behavioural studies led by Rawlins, have also used 'knockout' technology to investigate the role of glutamate receptors in learning and memory. They observed that whole brain deletion of GluA1 can cause deficits in LTP at CA3–CA1 synapses but, importantly, a behavioural dissociation between impaired spatial working-memory alongside intact reference-memory [75,76]. However, the LTP deficit in these mice may have been overestimated in the original study [77]. Nevertheless, that the deficit in spatial working memory can be rescued by transgenic expression of GluA1 on the knockout background is important [78]. This group has recently shown that GluA1 knockout impairs short-term spatial habituation but, surprisingly, enhances long-term spatial habituation [79]. These findings raise the possibility that the spatial working memory deficit in GluA1 knockout mice might be indirect, and reflect only the impairment in non-associative short-term habituation [80].

More recently, they have turned their attention to NMDA receptors using a cell-type and region-specific strategy, and observed that selective deletion of GluN1 in DG also causes the behavioural dissociation between spatial reference and spatial working memories [81]. A very recent paper using a new line of mice in which GluN1 is deleted in both CA1 and the DG again shows the relative sparing of spatial reference memory in the watermaze, but suggests that deficits can be observed if a beacon task is used which maximizes the opportunity for navigational interference, particularly when a path has to be inhibited [82]. The lesson from all these studies is that the specific type of memory being investigated has to be considered carefully with respect to the brain area targeted—a key argument of §2.

In addition to the glutamate receptor knockout studies described above, a wide range of genetically modified mice having mutations in different components of the postsynaptic machinery and downstream signalling molecules have been created. The now extensive list of mutated genes includes those coding for PSD scaffolding proteins [83], kinases and phosphatases [84–86], motor proteins [87,88], regulators for epigenetic mechanisms [89], translational regulators [9,90] and immediate early genes [91]. Interpreting the underlying complexity is difficult as some of these mutations have effects on the nervous system that go beyond changes specific to synaptic plasticity. In addition, simple monotonic changes in the expression or magnitude of synaptic potentiation concomitant to parallel changes in learning and memory are not always seen. While this may to some undermine the simplest versions of the SPM hypothesis, the vast majority of studies in which changes in synaptic plasticity are observed also show changes in memory in the mutant animals.

(c) Retrograde alterations

If synaptic weights are indeed the core substrate of hippocampal memory traces, alteration of the spatial distribution of synaptic efficacy across neurons and their dendrites within the hippocampus should interfere with memories of past events. Such 'retrograde alteration' can be achieved either by erasure of any learning-induced synaptic changes or by artificial induction of additional synaptic potentiation soon after memory encoding. The latter would effectively scramble the pattern of synaptic weights and thus render it behaviourally meaningless. As an example of this approach, Brun et al. [92] tetanized the perforant pathway input to the DG of rats trained

on a water maze reference memory task. As expected, induction of hippocampal LTP in vivo after 5 days of training resulted in a profound deficit in memory retrieval—an effect blocked by intraperitoneal administration of 3-(2-carboxy-piperazin-4-yl)propyl-1-phosphonic acid. By contrast, rats that received control stimulation of the same pathway showed normal memory of the hidden platform, indicating that NMDA receptor-dependent potentiation of hippocampal synapses interfered with the activated memory trace. If recently induced hippocampal LTP is followed by trains of low-frequency stimulation, enhanced field potentials often return to the pre-LTP baseline, effectively erasing the effects of the tetanus [93]. Though this phenomenon has, to date, only been used to depotentiate artificially induced LTP, it could in theory be used to reverse learning-induced changes at hippocampal synapses, as discussed in our previous review [38].

Sacktor's group have pursued the idea that a particular form of protein kinase C (PKC) may be involved in memory. They first showed that infusion of a peptide blocker of a constitutively active but atypical form of PKC (PKM-ζ) called ZIP could block LTP maintenance in vivo and abolish well-established place avoidance memory (figure 1f,g) [48]. These landmark findings relevant to retrograde alteration of synaptic efficacy were followed by papers implicating the role of PKM-ζ in maintenance of synaptic plasticity and memory in a variety of brain areas [94]. It therefore came as a surprise that PKM-ζ knockout mice are reported to have no deficits in plasticity and memory, while maintaining sensitivity to ZIP treatment [95,96]. Although these findings call the specificity of ZIP into question and, with it, the role of PKM-ζ as the quintessential 'memory molecule', they do not undermine the fact that a drug that causes a post-learning reversal of synaptic enhancement is associated with a complete erasure of a recently encoded memory (see Sacktor and co-workers' paper [97] in this issue). Recent work by Migues and Hardt is consistent with this association in demonstrating that PKM-ζ also maintains long-term memory for the location of recently explored objects in the rat hippocampus [98] and does so by regulating the trafficking of GluA2-containing AMPA receptors with memory strength positively correlated with post-synaptic GluA2 levels [99].

Some evidence points to another kinase, CaMKII, as a key player in LTP maintenance [86] in addition to its widely established role in LTP induction. Redondo & Morris [100] have implicated CaMKII as being on the pathway to the setting of synaptic tags—one essential step for lasting memory. Other work has shown that blocking the interaction between CaMKII and NMDA receptors with a CN21 peptide reverses hippocampal LTP in vitro [101], though it is yet to be demonstrated whether the same peptide interferes with maintenance of hippocampal memories. In line with the role of the CaMKII–NMDA receptor complex in maintenance of hippocampal plasticity and memory, 'knockin' mice with the NMDA receptor GluN2B subunit that is incapable of forming this complex show a deficit in consolidation of spatial reference memory [102]. The same animals also show a reduction of LTP magnitude on the Schaffer collateral/commissural-CA1 pathway, but we are not aware of any published data regarding a possible impairment of LTP maintenance in these animals.

(d) Mimicry

The creation of an artificial engram using a putative mechanism of memory formation would be a particularly stringent

test of the SPM hypothesis. The test in question would be to artificially introduce changes in synaptic weights in a distributed pattern and show that this results in a predictable display of 'memory' for something that in practice had either not happened or had happened earlier and then had been demonstrably forgotten. There is a pleasing irony here, for studies of false memory by neuropsychologists are generally seen as studies of how memory fails; for the neurobiologist, the possibility of artificially creating a false memory represents an intriguing experimental opportunity.

We may be getting very close to a true demonstration of mimicry in some brain structures with unambiguously defined CS and US inputs, most notably the amygdala in which learning follows Pavlovian principles (for review, see [14]). It is postulated that associative fear learning occurs through Hebbian LTP at synapses onto cells in lateral amygdala (LA). An association between CS and US occurs when cortical/thalamic projections carrying information about the CS fire coincidently with US-associated depolarization of postsynaptic LA cells. LeDoux's group demonstrated this using optogenetic stimulation of LA neurons at the time of tone delivery, which resulted in the formation of an artificial fear memory without the need for a foot shock [103].

The distributed-associative network of the hippocampus, on the other hand, makes designing a potential mimicry experiment much more difficult—and also brings out some of the key issues discussed in §2. One way of approaching the issue is to use learning to create a pattern, allow the memory to fade and be forgotten but hopefully not the molecular markers of its earlier existence. An analogy might be to the act of bringing back to life a ghost town in the wild west of America. But how might this resurrection of memory be achieved?

In recent years, optogenetics was developed as a way to control the activity of spatially and genetically defined populations of neurons with millisecond precision [31]. Coupling optogenetics to advanced temporal gene expression control systems enables one to tag a population of neurons active during a specific event and subsequently reactivate them at will. Tonegawa's group have used tetracycline-controlled transcriptional activation system to selectively express channelrhodopsin (ChR2) in those neurons of DG that were active during the encoding phase of a contextual fear conditioning task [104]. Crucially, tetracycline transactivator (tTA) was placed under the control of c-Fos promoter and ChR2 was controlled by the tetracycline-responsive element (TRE). As long as the mice were kept on doxycycline (Dox), expression of ChR2 was blocked by preventing tTA from binding to the TRE site. When taken off Dox on the day of critical memory encoding, ChR2 expression could be induced in DG neurons in an activity-dependent manner. Having expressed ChR2 in DG neurons that were active during engram formation, these investigators were able to reactivate the engram with light in a different context. Reactivation of the memory trace resulted in a robust increase in freezing behaviour—an observation consistent with fear memory recall. In a related approach, Mayford's group have described their use of the DREADD system to generate a synthetic memory trace [105]. Powerful and striking as these two landmark studies are, we believe that to fulfil the mimicry criterion of the SPM hypothesis, it is critical to move from the level of neuronal assemblies down to the level of synapses.

As suggested previously by Neves et al. [106], an experiment testing whether hippocampal NMDA receptor-dependent plasticity is sufficient for episodic memory could involve a hypothetical light or exogenous ligand-activated Ca^{2+} channel. As Ca^{2+} influx into the spine may be sufficient to induce early-LTP [107], activation of this Ca^{2+} channel once it has made its way to the spine should result in synapse-specific potentiation. Though a remotely controlled ion channel selective for Ca^{2+} has not yet been described, it is worth noting that some new ChR2 variants show enhanced Ca^{2+} conductivity [108] and it would be interesting to see whether activation of these channels within a dendritic spine could lead to LTP without the need for presynaptic activation.

In a 'dream experiment', the hypothetical Ca^{2+} channel would be expressed in all hippocampal neurons postsynaptic to the set of synapses under investigation, its transcription would be tTA-regulated and IEG-dependent, and the channel protein itself would contain a targeting sequence that directs it to recently potentiated (tagged) spines in the same way these synapses recognize plasticity-related products (PRPs) as outlined by the synaptic tagging and capture hypothesis [100,109,110] (figure 2a). Though we are beginning to unravel how PRPs like Homer-1a/Vesl-1S and Arc/Arg 3.1 are transported around the neuron [111,112], the precise mechanisms of PRP capture by tagged synapses remain elusive and will have to be uncovered before an experiment like this can be carried out.

The toolkit described above could in principle be used to study any IEG-expressing population of neurons in the hippocampus and beyond. The experiment outlined below focuses on principal neurons in the hippocampal area CA1 (figure 2b). The hypothetical channel would be expressed selectively at tagged synapses at the time of encoding (figure 2c), and these steps followed by forgetting and loss of the underlying memory trace (figure 2d). The question then is whether the trace could be brought back (figure 2e). Specifically, experimental animals would be trained in the presence of Dox on a one-shot spatial memory task in which the location of the goal—either a hidden platform in the watermaze [59], or the availability of food in a sandwell in the event arena [37]—changes every day. On a specific day, animals would be taken off Dox and subjected to strong memory encoding (figure 2b), which should induce IEG expression (and thus the Ca^{2+} channel) in hippocampal neurons (figure 2c). Animals would then be put back on Dox and the 'tagged' memory trace would be allowed to decay or would be overwritten by extensive training (figure 2d). The animals would then need to be tested to be confident that forgetting has occurred. The experimental question is then addressed by attempting to reintroduce this specific memory. This would be attempted optogenetically or pharmacogenetically with the effect that the only subset of synapses that would be potentiated would be those expressing the hypothetical Ca^{2+} channel and therefore those that were tagged during the critical memory encoding phase (figure 2e). If LTP at a specific set of hippocampal synapses is sufficient to construct a meaningful memory trace, re-inducing LTP via activation of this hypothetical channel should mimic weak memory of the correct location of the goal on the 'tagged' day.

One potential obstacle of such experimental set-up is protein turnover. Endocytosis and degradation of the hypothetical Ca^{2+} channel would lead to its progressive elimination from spines. Since by that time the synaptic tag would be long gone, selective redelivery of the channel protein to the spines of interest would be impossible. As mechanisms of protein degradation are being
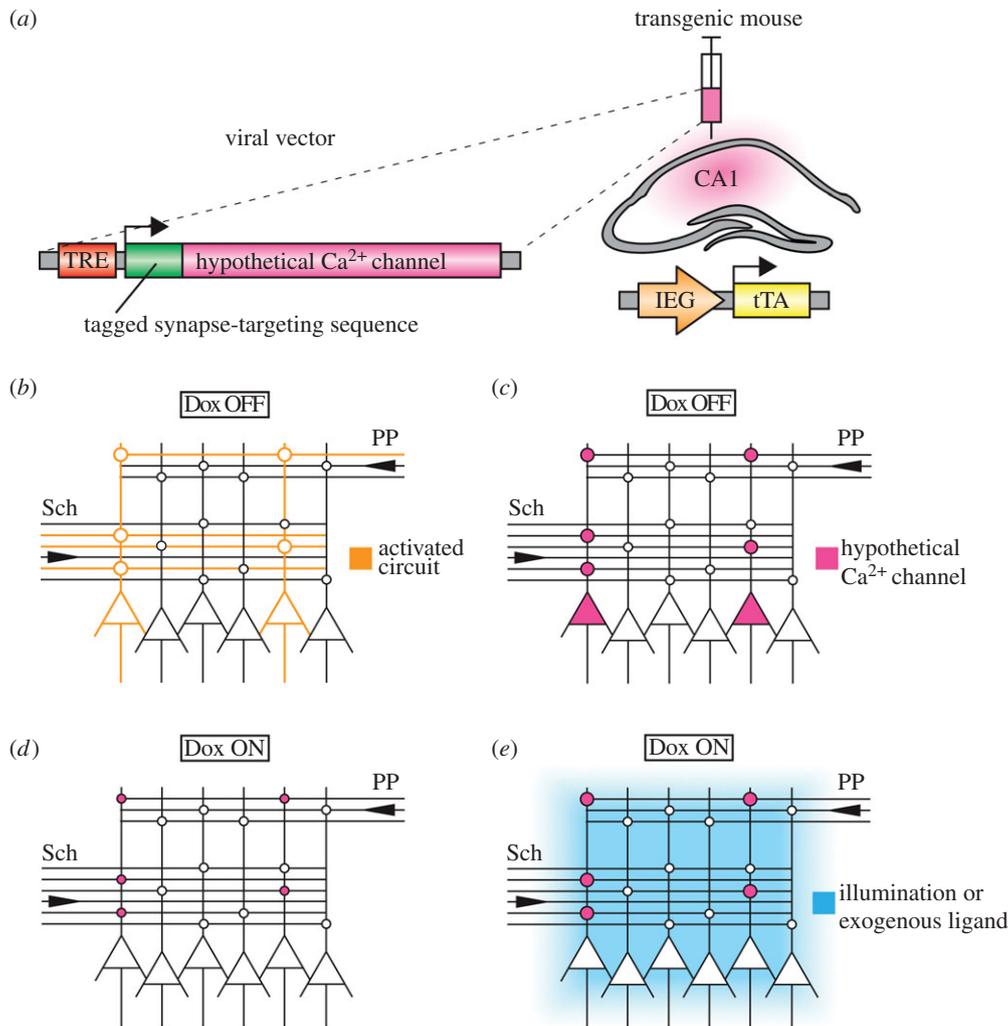
Figure 2. Hypothetical experiment testing the prediction that LTP at a given set of synapses is sufficient for engram formation. (a) Activity-dependent expression of hypothetical Ca²⁺ channel in hippocampal CA1 area. The IEG promoter-driven tTA transgenic animal is injected with a viral vector in which the hypothetical light- or exogenous ligand-activated Ca²⁺ channel with tagged synapse-targeting sequence is expressed in an activity-dependent and Dox-regulated manner. (b) Memory encoding in CA1. A specific pattern of activation of afferent fibres results in Hebbian LTP at a fraction of synapses onto CA1 pyramidal cells. (c) Synaptic tagging and capture. In absence of Dox, strong encoding results in formation of synaptic tags and synthesis of not only PRPs but also the hypothetical Ca²⁺ channel. The channel protein is then distributed around the neuron and captured by the tagged synapses. (d) Trace decay. The animal is put back on Dox. Synaptic potentiation at hypothetical Ca²⁺ channel-targeted synapses decays with time. (e) LTP reinstatement. Activation of the Ca²⁺ channel (either by illumination of the target area or infusion of the exogenous ligand) should result in LTP at synapses tagged during the critical encoding session. A successful mimicry experiment would involve a subsequent demonstration of retrieval of the reinstated memory trace. Sch, Schaffer collaterals; PP, perforant path.

increasingly understood [113], it might be possible to engineer the channel to resist various forms of cellular 'clean-up' and thus stay in the spine for a time period relevant to our proposed experiment.

4. The logical connection between the persistence of synaptic plasticity and the persistence of memory

A somewhat ironic feature of 'LTP' is its name. Synaptic potentiation outlasts the events of its induction and it can in exceptional circumstances be seen to last over a year [114], but in general LTP decays back to baseline within a few hours. Barnes used the differential rate of decay of LTP as a function of ageing in her pioneering studies of the relationship between synaptic plasticity and learning [12,115]. Other lasting forms of synaptic plasticity have also been observed, such as stimulus-selective response potentiation, which take some

hours to be expressed but are then persistent over time [116]. This instability of induction and persistence is problematic for the view that LTP-like changes in synaptic efficacy occur immediately and go on to mediate really lasting memory, albeit a puzzle that is complicated by the dual existence of both 'cellular consolidation' and the separate 'systems-consolidation' that enables one brain region to serve a time-limited role in bringing about lasting storage elsewhere in the brain (and most likely in the neocortex).

A systems perspective on this problem involves recognizing the interplay between cellular consolidation triggered within hippocampal neurons at the time of learning and systems consolidation between hippocampus and neocortex that comes into operation after learning (and is thought by many to involve sleep). New data at a systems level have emerged from the fMRI studies of LTP by Canals et al. [117]. They have shown that the induction of LTP in the hippocampal formation, and specifically the DG, is characterized by a larger BOLD signal at the monosynaptic site of potentiation but also by the appearance of a detectable change in BOLD

in other circuits, including the prefrontal lobe. This indicates that potentiation at one level may somehow be projected to or otherwise affect other levels of the neural circuit mediating memory processing. Preliminary data secured by Canals' group indicate that similar remote changes in neural activation occur following induction of LTP in CA1. The reason(s) for this systems aspect of LTP induction remain to be investigated, but could include an alteration in the excitation–inhibition balance following some types of LTP that is detectable through observation of a change in the coupling of excitatory post-synaptic potentials to population spike generation in field-potential recordings. The work of Canals and co-workers (see [118] in this issue) discusses LTP-induced alterations in feed-forward disinhibition.

A separate cellular consolidation possibility is that early-LTP decays precisely in order to re-set hippocampal circuits back to a level whereby they can most effectively process new information at a later time—not least the same day. This gets round the need for lasting potentiation within the hippocampus, though it is of course still necessary in the neo-cortex, but also raises the issue of the timeframe for which information must be retained by cellular consolidation for the systems-consolidation aspect to work effectively.

Central to addressing this issue is the work of the Magdeburg group of Matthies and Frey that established the separate existence of early- and late-forms of LTP, the latter being defined as protein synthesis-dependent. Their work provided the first experimental evidence suggesting that neuromodulators, especially dopamine (DA), play a significant role in gating of plasticity and memory persistence. *In vivo* and *in vitro* electrophysiological studies have revealed a specific role for DA in control of temporal persistence of LTP [119–122]. Pharmacological manipulations of DA receptors also indicate that DA is required for the persistence of memories in the hippocampus [123–125]. DA receptor activation can lead to enhanced somatic and dendritic protein synthesis essential for the establishment of lasting plasticity and memory [126,127]. This function is mediated by protein kinase A, extra-cellular-signal regulated kinase (ERK) 1/2, CaMKIV and cAMP response element-binding protein CREB [128–131].

The midbrain dopaminergic neurons of the ventral tegmental area (VTA) project to the hippocampal formation [132,133] and are thought to release DA under circumstances of novelty or surprise [134,135]. In addition, a recent paper suggests that noradrenergic (NA) terminals of the locus coeruleus (LC) might have a role in DA transmission in the hippocampus [136]. The necessity of DA-dependent mechanisms within hippocampal neurons in cellular consolidation implies that cellular consolidation depends not just on the intrahippocampal, cellular processes, but also on the action of systems-level components. Therefore, we propose that 'cellular consolidation' is renamed 'initial consolidation'.

There are many lines of evidence suggesting that the persistence of memory is determined largely by neural activity that occurs at the time of memory encoding. However, the synaptic tagging and capture hypothesis of protein synthesis-dependent LTP developed by Frey & Morris [109,110] offers the intriguing but distinct perspective that the persistence of memory is also dependent on *independent* neural activity afferent to the same pool of neurons mediating LTP that occurs before or after memory traces are encoded. According to this hypothesis, the local setting of 'synaptic tags' at activated glutamatergic synapses during memory

encoding can be dissociated from DA-dependent synthesis and distribution of PRPs that is induced by surrounding events. PRPs are then captured by synaptic tags in order to stabilize synaptic change—a process that is critical for initial consolidation.

Until recently, a challenge for the synaptic tagging and capture hypothesis has been to assess its relevance to real memory. Considering that exploration of a novel environment probably activates VTA DA neurons to release DA in the hippocampus and thus cause upregulation of IEGs such as Arc and Homer-1a [137,138], the synaptic tagging and capture hypothesis predicts that unrelated novelty exploration before or after memory encoding should enhance the persistence of a recently encoded memory [139]. This prediction was first confirmed using a hippocampus-dependent inhibitory avoidance task in rats [140]. Moncada and Viola showed that weak memory could be consolidated into long-term memory by unrelated exploration of a novel environment. This novelty-induced memory persistence was blocked by intra-hippocampal injection of DA D_1/D_5 receptor antagonist and β-adrenergic receptors antagonist [140,141] or by inhibition of induction or expression of CA1 LTD [142]. Complementary results have been obtained using different learning tasks including taste memory, spatial object recognition, contextual fear conditioning and spatial memory [37,143,144].

Our laboratory has developed a realistic everyday appetitive paradigm for rats in order to establish whether unrelated novel experiences can facilitate the persistence of reward-motivated spatial memory [37]. We have expanded our analysis to different systems domains and, for this purpose, have recently altered the protocol for the spatial memory task in the event arena and made it suitable for mice (figure 3a). The object of switching the task to mice is to enable genetically modified animals to be tested. The tyrosine hydroxylase-Cre knockin mice with C57BL/6 genetic background [145] were trained on this one-shot spatial memory task over four weeks. The mice have to learn a different location of food each day and, with five sandwells to choose from, performance increases quite rapidly from the chance level of two errors on the daily choice trial to a consistent pattern of less than one error per day (figure 3b). A series of post-learning tests, of which we here show only one, established that: (i) persistence of one-shot memory depends on reward magnitude, lasting only 1 h with two pellets but 24 h with eight pellets; (ii) 5-min exploration of an open field with a variable novel floor substrate 30 min after weak two-pellet encoding successfully transformed 1-h memory into 24-h memory (figure 3c) and (iii) pharmacological interruption of DA D_1/D_5 receptors, but not β-adrenergic receptors in hippocampus during novelty exploration prevented novelty-induced memory persistence over 24 h. Those characteristics are consistent with our earlier rat data [37]. The next step is to substitute novelty exploration with photo-activation of VTA DA neurons or LC NA neurons using optogenetics (figure 3d). With this procedure, our prediction is that activating these neurons in some appropriate temporal pattern should convert a recently encoded short-term memory into a long-term memory.

5. Conclusion

Martin *et al.* [16] laid out a framework for testing rigorously the widely held notion that synaptic potentiation and
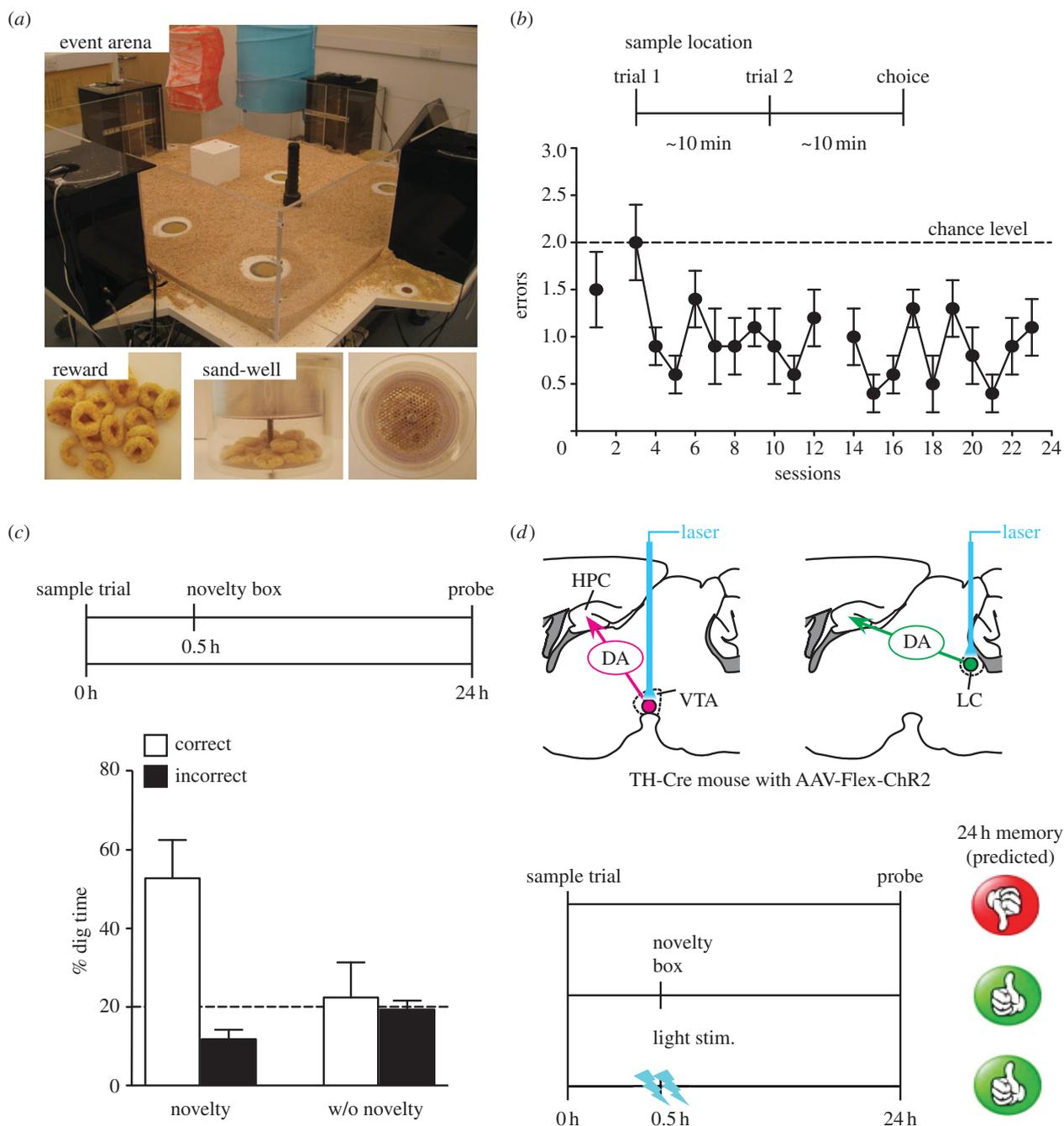
Figure 3. One-shot spatial memory task on the event arena for mice. (*a*) Event arena for one-shot spatial memory task. The event arena during a daily choice phase. Five sand wells are open but only one contains the reward pellets. All open sand wells contain several pellets that are inaccessible to the mouse in order to control for olfactory artefacts. (*b*) Daily spatial memory performance (errors). Every day mice have two trials to encode the new sand well location, followed by a choice phase. They quickly reach a stable performance level of less than one error (with two errors being the chance level). (*c*) Novelty-induced enhancement of memory persistence. Critical sessions involve one sample trial followed by an unrewarded probe test 24 h later. 5 min exploration of a novel environment 30 min after encoding results in enhanced persistence of one-shot spatial memory, as demonstrated by increased dig time in the correct location. (*d*) Prediction of memory enhancement by optogenetic stimulation of catecholaminergic nuclei. We predict that photoactivation of DA cells of the VTA or DA-releasing NA cells of LC in TH-Cre mice injected with Cre-dependent ChR2 virus (AAV-Flex-ChR2) after weak memory encoding will result in enhancement of memory persistence that mimics the novelty effect. Error bars, $\pm$ s.e.m; dotted lines, chance level.

depression are key players in mediating the creation of memory traces or engrams. That framework has stood the test of time, with exciting new approaches using contemporary techniques exploring the idea further with respect to *detectability*, *anterograde* and *retrograde alteration*. Perhaps most exciting are the first steps being taken towards testing and possibly satisfying the *mimicry* criterion using optogenetic and other cell-type-specific molecular tools. Critical experiments remain to be done, but the neuroscience community can justifiably feel tantalizingly close to having tested one of the great ideas of modern neuroscience. Forty years on, LTP continues to excite us all as it slowly gives up its mechanistic secrets and reveals its important functional role in learning and memory.

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