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Spatial memory and hippocampal enhancement

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Given the central role of hippocampal function in spatial and episodic memory, the concept of enhancing it when compromised is attractive. This might be realised behaviourally, pharmacologically or via more radical routes such as brain stimulation. Successful approaches in each of these domains include trial-spacing, rest, and NMDA or cholinergic receptor modulation, but the goal of enhancement has to be clear as some approaches can enhance in one domain but inhibit in another. Enhancement may also extend the duration of memory rather than augment encoding, an idea conceptually embedded into the synaptic-tagging-and-capture theory of memory persistence. In addition, recent work on human spatial memory reflects new findings about the interacting components of egocentric and allocentric processing of human navigation.

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Introduction

The famous opening sentences of O'Keefe and Nadel's (1978) book '**The hippocampus as a cognitive map**' [1••] remind us of the importance of spatial memory: '*Space plays a role in all our behaviour. We live in it, move through it, explore it, defend it. We find it easy enough to point to bits of it: the room, the mantle of the heavens, the gap between two fingers, the place left behind when the piano finally gets moved.*' In 2015, shortly after the award of the Nobel Prize for the discovery of place and grid cells (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2014), we have good reason to celebrate the progress that has been made by systems neuroscientists in understanding spatial memory.

Our story begins, however, with the earlier discovery of the critical role of the hippocampal system in human memory [2••]. This triggered an explosion of research leading to our present understanding of hippocampal function and its role in memory. Aspects of this work have enabled translational research and drug discovery with the aim of improving cognition, including spatial memory. Such work forms one part of a wider project to support the 'mental wealth of nations' [3•]. Memory enhancement has been discussed in the context of more effective attention, better encoding or consolidation of information and, although less frequently, of improving memory retrieval. There are mechanistic implications of each of these distinct processes (Box 1). Post-trial enhancement of consolidation has been a longstanding theme of memory research [4]. More recently, the opportunity for exploiting new advances in the molecular neurobiology of memory has been raised [5], and a strong case advanced for paying more attention than hitherto to the mechanisms of activity-dependent synaptic plasticity, such as long-term potentiation [6•]. Molecular insights and synaptic plasticity offer potentially important neurobiological anchors to behavioural observations.

Within the spatial domain — the specific focus of this contribution — there is the prospect of enhancing spatial memory in everyday life. This would include helping older people remember where things are around the house through to preventing them from getting lost when finding their way. More effective spatial memory and navigation involve a number of interacting processes and mechanisms including remembering the location of a goal, planning a route, greater flexibility in coping with unexpected detours and so on. Exploring this in animal models, and more recently humans also, has been guided by neuroscience discoveries such as those of place cells [7••], head-direction cells [8••], and grid-cells [9••]. Collectively, these provide a neural structure for spatial memory. Whether such a finely tuned system, dependent on intricate excitatory and inhibitory circuitry [10,11], can reliably be enhanced is unclear.

However, spatial memory and other types of 'memory space' [12], do surely serve to anchor and enhance other aspects of memory. There is a long history of methods, such as the '*method of loci*' celebrated in Frances Yates

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classic book 'The Art of Memory' [13], in which people train themselves to use buildings or towns with which they are familiar to provide a structure for remembering the content and sequence of new information. This was a favoured method of orators in remembering their speeches, and used to this day by people who perform extraordinary memory feats (such as remembering absurdly long numbers). Other behavioural 'tricks' involve the disciplined use of existing mental structures or schemas to organise new information, or the imposition of a short rest after learning. However, the discipline of doing these (even though they work) is beyond most people.

The usual assumption about enhancement is that, behavioural approaches aside, a pharmacological intervention might be found such as a nicotinic partial agonist (e.g. of the α7 subunit) or a phosphodiesterase inhibitor (e.g. of PDE4). Considerable efforts are being made in pharmaceutical and biotech companies to develop such compounds, with a major focus on improvement of cognitive dysfunction in neuropsychiatric conditions [14•]. '*Enhancement*' induced by such drugs is likely mediated by mechanisms that potentiate some plasticity-related mechanism (such as increased membrane excitability or protein-synthesis). However, there are other possibilities such as improved signal-to-noise ratio of target relative to interfering material rather than 'bigger' in a literal sense — as in the process of pattern separation that might be affected by the balance between excitation and inhibition in the dentate gyrus. In addition, a memory might be enhanced in the sense of being more persistent over time than stronger at the time of encoding. Indeed 'strength' and 'persistence' may be orthogonal parameters with distinct possibilities for behavioural or pharmacological interventions.

In effect, the goal of enhancement is context-dependent — what is the specific aim of altering some cognitive process? We next illustrate some relevant complexities with reference (a) to work on D-cycloserine and NMDA receptors [15••], and (b) to the contribution of synaptic tagging and capture (STC) to the place of enhanced protein-synthesis in memory enhancement [16,17].

Complexities and assumptions

The simple theme of this section is to point out that 'bigger is not always better' (Box 1). This is not to imply that enhancement is not possible and certainly not to

Box 1 Enhancement of spatial memory: concepts and putative mechanisms

Enhancement includes memory traces being stronger (mechanistically due to enhanced synaptic plasticity), but there are other possibilities. These include, firstly, improved signal-to-noise ratio of target relative to interfering material (due to more effective pattern separation by the dentate gyrus via alterations in excitatory-inhibitory balance, or neurogenesis); secondly, more effective persistence over time (due to capture of plasticity-related proteins [PRPs] at tagged synapses).

Spatial memory refers to memory of the places of events or things in the world, and can include paired-associate and map-like representations, representations of the value of the sought object, and/or of the route that should be taken to get from the present location to a remembered location. In this respect, spatial memory is generally considered a 'catch-all' term for diverse aspects of spatial learning and navigation.

Encoding, storage, consolidation, retrieval refer to successive stages of the processing of information entering long-term spatial memory. *Encoding* is the process of transforming perceptual information into single or associated items into memory traces. Effective encoding may involve pattern separation and filtering of target relative to interfering material. *Storage* is the process by which such traces last over time — usually thought to be a passive process involving an initial alteration of synaptic strength that is distributed across synapses and neurons in DG, CA3 and CA1. *Consolidation* is the further process that helps ensure that stored information is less likely to decay over time, that is, to become stabilised. This is likely a process where enhanced synthesis, distribution and utilisation of plasticity-related gene products will be especially important. *Retrieval* refers to the putative process by which neural activity interacts with stored traces and so, possibly engaging pattern separation, re-activates representations that, at least in humans, have the phenomenological experience of implicit or explicit remembering. Retrieved information may affect processing speed or choice in the absence of awareness, or it may enter consciousness in an explicit manner and so constitute an experienced event. Retrieval of, for example, context fear conditioning has been shown to affect immediate early gene activation in diverse brain areas, with the areas preferentially activated changing with the passage of time.

The hippocampal formation consists of the entorhinal cortex, dentate gyrus, CA3, CA1, and subiculum (Andersen *et al.*, 2007). There is debate about whether the medial and lateral septum should be considered part of the hippocampal formation, but the importance of the cholinergic and GABAergic modulatory input via the septum, particularly in relation to encoding, cannot be ignored. Mechanistically, nicotinic agonists and GABAergic inverse agonists act by altering membrane depolarization at the time of memory encoding. Dopaminergic modulation is relevant because of the importance of D1 receptor signalling for the persistence of hippocampal synaptic plasticity and memory, possibly acting via the pKA-cAMP pathway, DARPP-32 and inhibition of protein phosphatase 1 (PP1). Importantly, the hippocampal formation does not work in isolation — it works in partnership with numerous other brain areas, including the neocortex for systems memory consolidation, such that enhancement of hippocampal memory processing may have its impact in other brain areas where memory traces may be stored. The mechanisms of 'initial' or cellular consolidation impact on the effectiveness of subsequent systems consolidation.

Animal model refers to any animal based research strategy usually using *Drosophila*, rodents or non-human primates, often using interventional approaches that are ethically impossible in humans. The supposition is that memory processing has evolved over time, retaining many features that are quite old in evolutionary terms and that therefore can be successfully investigated in animal models. However, we should be sensitive to many differences between humans and animals — including anatomy, language and prior-knowledge — that may collectively impact successful translation of cognitive enhancing drugs from animal proof-of-concept studies through to phase 3 studies in humans. The puzzle of 'lost in translation' is important in drug development.

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suggest that it is in any sense undesirable; rather to recognise the need for specifics with respect to what could or can be enhanced, and for a fuller understanding of mechanism in the design of effective drugs.

One example relates to the potentially enhancing effect of D-cycloserine (DCS), a partial agonist at the strychnine-insensitive glycine receptor associated with the NMDA receptor (the GlyB site). Electrophysiological studies have indicated that DCS works by augmenting the action of NMDA receptors [18], but that high doses or repeated administration can result in de-sensitization and loss of effect [19]. Numerous facets of learning and extinction have been investigated, with studies of the extinction of fear (itself a learning process) being particularly promising regarding the effectiveness of DCS in promoting extinction (i.e. loss of fear) in both animal models and human studies (see meta-analysis of published work [15••]). It has long been apparent that DCS can improve spatial learning and memory, particularly in aged rats [20]. New findings suggest that it can also enhance the latent extinction of a spatial task, apparently by enhancing the expectation that a spatially defined goal no longer has reward available [21•]. A 'latent' procedure is of particular interest therapeutically as it explores whether the valency of a goal (or fear) can be altered outside the context in which it is normally experienced. Interestingly, this new work on DCS and spatial memory also investigated an extinction-like process.

However, if DCS acts as a partial agonist by enhancing NMDA receptor function — *promoting* activity-dependent synaptic plasticity — we have the paradox that there are circumstances in which NMDA *antagonists* can themselves be beneficial. NMDA antagonists block the induction of hippocampal LTP, long-term depression (LTD) and memory encoding — all thought to be mechanistically related [6•,22]. However, the maintenance of LTP and of previously established memory storage may be another matter. For example, it has been shown that daily post-induction blockade of NMDARs can reduce or even block the decay of LTP across days [23]. Correspondingly, continuous post-training intrahippocampal application of the NMDA receptor antagonist D-AP5 over 7 days enhances the retention of watermaze spatial memory over periods of 7–14 days [24]. While this may be associated with reduced interference due to the failure to learn new competing information, an alternative possibility suggested by these authors is blockade of NMDA receptor-dependent long-term depression (LTD). The paradox is that encoding processes that are *enhanced* by an NMDA receptor partial agonist (LTP, memory encoding) create memory traces that are then *sustained* by NMDA receptor blockade (block of LTD, block of extinction). This is a 'Catch-22' and one lesson of these studies is that cognitive enhancement has to be understood within context. Is the specific aim to enhance memory encoding, or retention, or even retrieval? Different pharmacological strategies may be appropriate in each case. The now widespread use of DCS for the extinction of anxiety is a good example of a highly specific use.

Our second example relates to how increased synthesis of plasticity-related proteins (PRPs) could enhance the temporal persistence rather strength of memory [25]. Protein-synthesis has long been thought to be important for the persistence of memory, although the idea has not been without criticism in recent years [26,27]. Separate from discovering the identity of the PRPs responsible, and the mechanisms by which their availability affects neurons, there is the issue of how diffusely synthesised PRPs find their way to the specific synapses involved in one memory trace rather than another. The 'synaptic tagging and capture' hypothesis, developed originally in the context of LTP [16], but now extended to behaviour [28,29•], asserts that individual synapses carry a temporary 'tag' marking that they have recently been potentiated or depressed. This tag, which may be a transitory structural change of the synapse [30], serves then to sequester plasticity related proteins (PRPs) that are synthesised somatically or in local dendritic domains [31••]. This sequestration stabilises synapses. Given that there are two separate but interacting processes (tag setting; PRP synthesis, diffusion and capture), the STC framework raises the intriguing prospect that these could be induced at different times — an idea not always considered in discussions about the relevance of LTP to enhancement [6•]. Interestingly, a later article from Gary Lynch's group queries the relevance of protein synthesis to memory persistence despite replicating the basis 'synaptic tagging and capture' finding [32]. Specifically, these authors suggest that the availability of PRPs should normally be sufficient given the level of ongoing neural activity, and that the specific triggering of PRP synthesis is only likely to be relevant in circumstances of aberrant neural deprivation.

Work on 'behavioural tagging' raises a disquiet for this suggestion [28,33•]. One pertinent study established that, even if the encoding of spatial memory created memory traces that demonstrably lasted for less than one day, pre-training or post-training novelty exposure that independently up-regulates the availability of PRPs could enhance the duration of such memories to at least 24 hours [34•]. Such a memory is not stronger at a short delay, but it does last much longer (24 hours). Comparison of electrophysiological and behavioural data (Figure 1) reveals an analogy between theta-burst induced LTP, which decays gradually to baseline over 10 hours, and the daily forgetting of a weakly encoded memory. The novelty-induced enhancement at 24 hours is clear. The animals in these experiments were in no plausible sense suffering 'aberrant neural deprivation' as they successfully performed behavioural tests everyday. If PRPs are ordinarily at a sufficient level, as Lynch *et al.*

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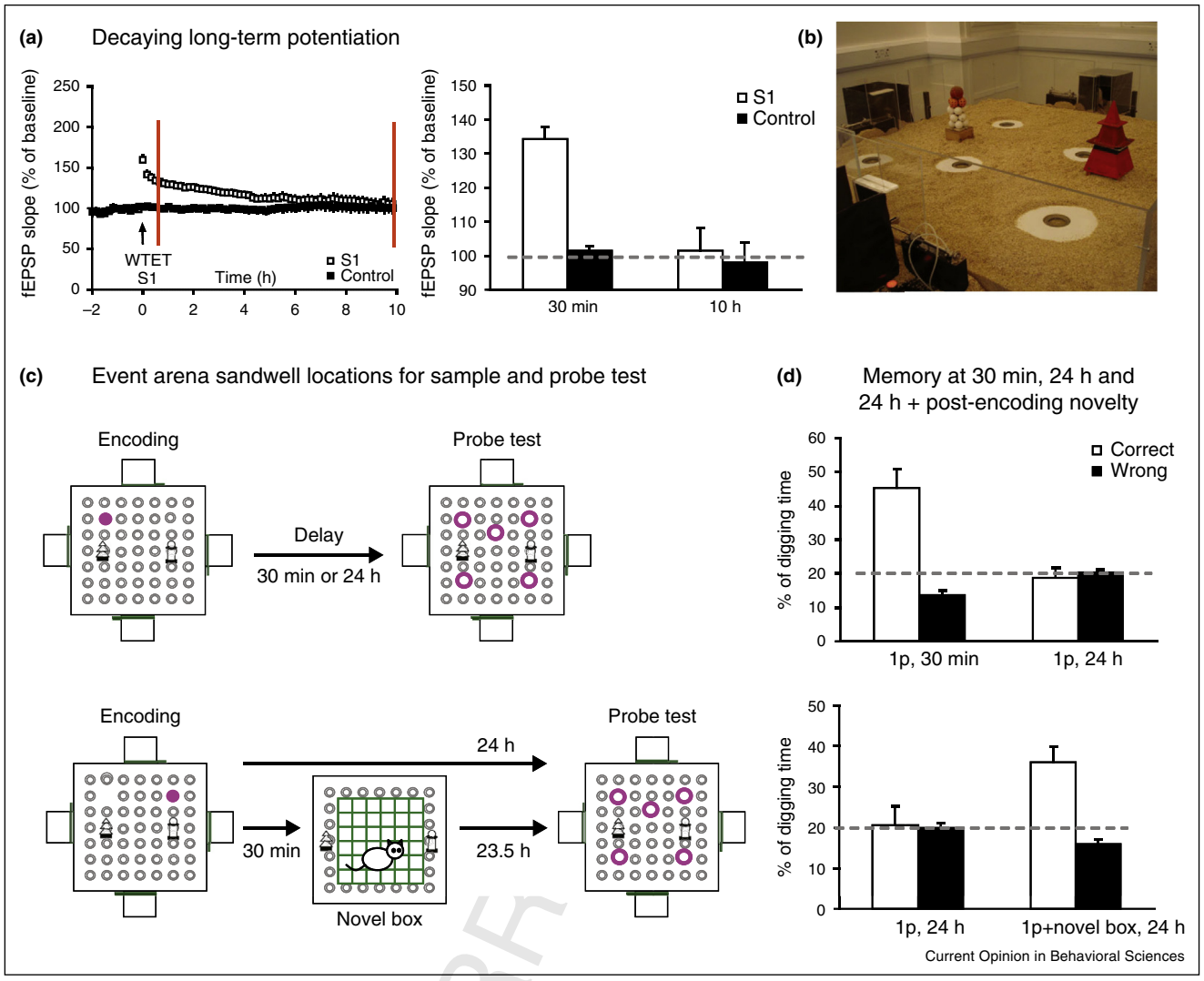
Figure 1



Electrophysiological and behavioural studies of synaptic tagging and capture: **(a)** Electrophysiological brain slice experiments reveal the decay to baseline of theta-burst induced LTP when recording continues for a sufficient length of time. Red lines indicate points at which bargraph data is plotted. **(b)** The 'event arena'. **(c)** Experimental designs for within-subject 'everyday spatial memory' experiments in which rats learn and then forget a different spatial location each day. Locations to remember shown by way of illustration include Row 2, Column 2 and Row 2, Column 6, with up to 47 possible locations across days. **(d)** Bargraph shows effective memory at 30 min, forgetting over 24 h, and the induction of more persistent memory by post-trial novelty. Based on Wang *et al.* (*Proc. Natl. Acad. Sci.* 2008 — Ref [31••]).

[6•] argue, there is no reason why post-encoding novelty (known to drive immediate early genes) should enhance the persistence of memory in an anisomycin-sensitive manner. A D1/D5 receptor antagonist into the hippocampus also blocked the post-trial enhancing effect of novelty. These findings have important implications for cognitive enhancement and for the mode of action of putative enhancers targeting plasticity that are in development (including PDE4 inhibitors).

Enhancement may also be achieved non-pharmacologically by altering the type of training required to yield a persistent memory. Memory is generally more persistent if induced by multiple training trials, particularly when they are spaced apart than massed together. This fundamental principle of human memory was first described over 130 years ago by the German psychologist Herman Ebbinghaus [35], and has since been endorsed in both invertebrate and vertebrate animal models. In the fruit fly *Drosophila melanogaster*, for example, a single session of associative olfactory avoidance conditioning will yield a memory immediately after training, but this memory will decay completely within 24 hours. When conditioned with ten massed training sessions, memory will last for

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about one day. But when such training sessions are spaced by 10–15 min, memory will last for up to one week [36]. This persistent memory depends on protein synthesis and CREB [37]. Importantly, memory persistence after one-session learning is enhanced by over-expression of a CREB activator in flies, indicating that mechanisms of consolidation can be facilitated to induce stable memory with less training, and such effect may be achieved pharmacologically as well [38,39•]. In rodents, spatial memory persists for 24 hours or longer if three encoding trials are spaced by 10 min in a delayed match-to-place version of the watermaze, but not if training trials are massed [40•]. Thus, the persistence of spatial memory also depends on the temporal specifics of encoding. Memory can be enhanced by either optimising consolidation behaviourally (such as by allowing a rest between training trials [41]), or might be helped pharmacologically by pairing suboptimal training with a consolidation enhancer (for example a PDE4 inhibitor). It should be noted, however, that the finding following rest in humans and the prediction with the drug is a more persistent rather than a stronger memory per se.

Examples of putative enhancers

Now that more than 50 years have passed since the discovery of Scoville and Milner, has there been progress towards a drug to treat memory deficits? We now discuss examples of putative enhancers, including their respective impact on spatial memory in animal models.

Ongoing clinical and pre-clinical research efforts within the pharmaceutical industry have been discussed in relation to treatments for cognitive dysfunction [14•]. These efforts led to the development of selective partial agonists of the α7 nicotinic receptors (CHRNA7). α7 receptors are Ca^{2+} permeable ligand-gated ion channels and they are key components of cholinergic neurotransmission. Clinical results have been achieved with partial agonists such as TC-5619 (Targacept), which was reported to improve executive function in schizophrenic patients with additional benefits in measures of working memory in nicotine users [42]. Another clinical stage α7 partial agonist — EVP-6124 (Forum Pharmaceuticals [43] — facilitates the persistence of object recognition memory in rats when dosed pre-trial or post-trial, suggesting that activation of α7 nicotinic receptors may contribute to memory consolidation [44•]. One study found that the late phase of CA1 LTP is enhanced in a protein synthesis-dependent manner by the α7 partial agonist SSR180711 [45]. However, the drug also affected post-tetanic potentiation suggesting that the effect on L-LTP was indirect, possibly via increased depolarization during induction. The critical experiment of applying SSR180711 after LTP induction was not performed.

Spatial memory enhancing properties have, to our knowledge, not yet been described in rodents or humans for this class of drugs. CHRNA7 knockout mice are unimpaired in tests of spatial reference memory in the watermaze [46], and exhibit only minor deficits in a delayed match-to-place test [47]. In contrast, these mice made more omission errors in the five-choice serial reaction time test indicating impaired attention [48,49]. Interestingly, a 2 base pair (bp) deletion in exon 6 of the CHRFAM7A gene (a partial duplication of CHRNA7) with presumed dominant negative effects on α7 was associated with poor delayed recall in the Wechsler memory scale test of logical memory, suggesting an α7 contribution to human memory [50]. However, clinical tests of logical memory typically do not differentiate between memory encoding and consolidation, because immediate and delayed recall is tested within minutes, rather than hours or days. The role of CHRNA7 receptor system for episodic memory in humans is therefore not yet well understood, while animal data and clinical trial data on α7 partial agonists clearly point towards contributions to attention and executive control.

A somewhat clearer picture emerges when looking at a second class of compounds with putative effects on the encoding of memory, the inverse agonists of the GABA α5 subunit. GABA receptors, which are heteromeric complexes comprised of α, β, and γ subunits, are ligand-gated chloride channels that modulate inhibitory tone throughout the CNS. Non-selective inhibition of GABA-receptors to enhance neuronal firing during memory encoding is not feasible due to seizure liabilities. However, the α5 subunit of the GABA receptor is localised primarily to the hippocampus of the mammalian brain where is contributes to roughly 20% of GABA currents [51,52,53•]. The action of an α5 selective inverse agonist, therefore, would be to partially release tonic inhibition of hippocampal pyramidal neurons just enough to increased neuronal excitability during memory encoding, but not enough to cause a seizure. Performance in the delayed match-to-place version of the water maze is improved in mice lacking α5 subunits [53•]. The same mice exhibit a reduction in spontaneous (but not evoked) IPSCs in the hippocampal CA1 area and increased paired-pulse facilitation (PPF). Pharmacological inhibition of α5 by the selective and highly potent α5 inverse agonist MRK-016 facilitates PPF and theta-burst LTP, and it enhances 4 hours spatial memory in rats [54••]. Similarly, L-655,708 has been shown in rats to facilitate theta-burst LTP, acquisition of an escape strategy, and spatial search accuracy measured 15 min post-training in the watermaze [55]. Neither compound has either pro-convulsive or anxiogenic effects as observed with non-selective inhibitors of GABA receptors. L-655,708 did not advance to the clinic. And although MRK-016 was well tolerated at doses up to 5 mg in young healthy volunteers, clinical trials were terminated due to adverse effects in elderly subjects [54••].

Dopaminergic signalling serves diverse functions in different neural circuits (see interview with Trevor Robbins

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— http://www.dnalc.org/view/812-The-Dopamine-System.html). In the hippocampus, it is central to the persistence of spatial memory and synaptic plasticity [34•,56,57,58•]. The effects of dopamine on D1/5 receptors are counteracted by phosphodiesterases that rapidly hydrolyse cAMP, such as PDE4 — a target considered for cognitive enhancement for more than 20 years. PDE4 has been implicated in the regulation of DARPP-32 phosphorylation, inhibition of protein phosphatase 1 (PP1), AMPA receptor trafficking, and the regulation of transcription [59•,60•]. The prototypical PDE4 inhibitor Rolipram enhances memory in mice and rats when dosed pre-trial and post-trial, and its effects have been demonstrated in various tests of memory including contextual conditioning [61], object recognition [62,63•], and object location memory [64]. Rolipram facilitates the late phase of CA1 LTP when present during stimulation [61,65], an enhancement that is dependent on protein synthesis. Interestingly, the Rolipram-induced enhancement of LTP in one population of synapses was found to be sufficient to rescue LTP persistence in an independent weakly potentiated population of neighbouring synapses [65]. The latter finding is consistent with a mechanism of enhanced synaptic tagging and capture. Unlike long-lasting LTP induced by strong pre-synaptic input alone, however, Rolipram-enhanced LTP is insensitive to inhibitors of D1/D5 dopamine receptors, suggesting that this drug bypasses the necessity of D1/D5 receptor activation for LTP [65] (Figure 2).

Rolipram is not suitable for clinical development because of a narrow therapeutic index with unwanted side effects such as emesis and gastrointestinal complications. Two PDE4 inhibitors have been approved by European and US regulatory agencies — Roflumilast (Forest Pharmaceuticals — http://www.frx.com) as an anti-inflammatory agent for chronic obstructive pulmonary disease (COPD); and Apremilast (Cellgene — http://www.celgene.co.uk) for the treatment of psoriatic arthritis. Both compounds have the potential to cause emesis and their efficacy in models of memory is unclear. Next generation PDE4 inhibitors with a lesser emetic potential have been developed for CNS indications, such as the allosteric modulators of PDE4 (deCODE [66]) and HT-0712 (Dart NeuroScience). The clinical stage compound HT-0712 enhances contextual long-term memory in normal young mice when dosed 20 min prior to training or 1 hour after training, but it has no effect when dosed 3 or 6 hours after training [67••]. These temporal specifics of post-trial efficacy of HT-0712 overlap with the development of a protein-synthesis dependent phase of memory after fear conditioning [68]. A higher-than-normal dose of HT-0712 is required to enhance memory retention in mice harbouring mutant CBP (CREB binding protein), indicating that PDE4 modulation of memory persistence is linked to transcriptional regulation *in vivo* [63•]. These findings support a mechanism of enhanced CRE-mediated gene-expression and enhanced memory persistence via PRPs. In addition HT-0712 was shown to improve associative fear conditioning, spatial reference memory, and the induction of the CREB target gene BDNF in aged mice, suggesting that it may be effective to treat age-associated memory problems including spatial memory deficits in humans [67••].

Effects of PDE4 inhibitors on human memory are now being evaluated in clinical settings. With regard to the design of such human clinical studies, careful consideration must be given to the mechanism of PDE4 inhibitors to enhance memory persistence. Clinical tests of memory included within the ADAScog and the Wechsler Memory Scale typically assess working memory and short-term memory within seconds (immediate recall) or minutes (delayed recall) of learning. Such retention intervals are appropriate to capture the effect of drugs on attention or memory encoding, but less so for longer lasting processes. Investigators might be misled by the failure of a drug to work if the mechanism is via consolidation taking place over many hours. It will be important to ask specific questions and to consider the mechanism of action of novel drugs so that clinical trials can be designed accordingly. Complex tests of spatial memory and navigation are rarely included in clinical trials, but they may be particularly suited for early detection of memory problems associated with MCI and Alzheimer's disease, because of the impact that these conditions have on the entorhinal cortex early on [69].

Studies in humans and non-human primates

The translational aim of animal studies is to develop drugs or other procedures for humans. One step can be the use of non-human primates as an intermediary between rodents and humans, such as work revealing the positive effect of an Ampakine (CX-717) on recognition memory together with a reduction of the negative effects of sleep deprivation [70••]. While we are unaware of studies of spatial memory in monkeys using a putative cognitive enhancer, allocentric spatial memory in monkeys appears also to be hippocampal-dependent [71]. Interest in real-world navigation in monkeys using mobile devices, and perhaps aided by 'view cells', sets the stage for relevant investigation [72•,73].

The more radical strategy of electrical stimulation has also been tested in monkeys. Recordings of memory activity-dependent networks in hippocampal CA3-CA1 subfields were analysed using a multi-input multi-output (MIMO) algorithm developed by Ted Berger of the University of Southern California, and then played back by way of stimulation to these networks. The results revealed striking changes in cell-firing associated with the encoding of object and spatial versions of a delayed matching-to sample task with trial-unique stimuli, and evidence that stimulation could specifically enhance 'difficult' trials [74•]. The longest delays tested were of 40 s, and therefore it seems

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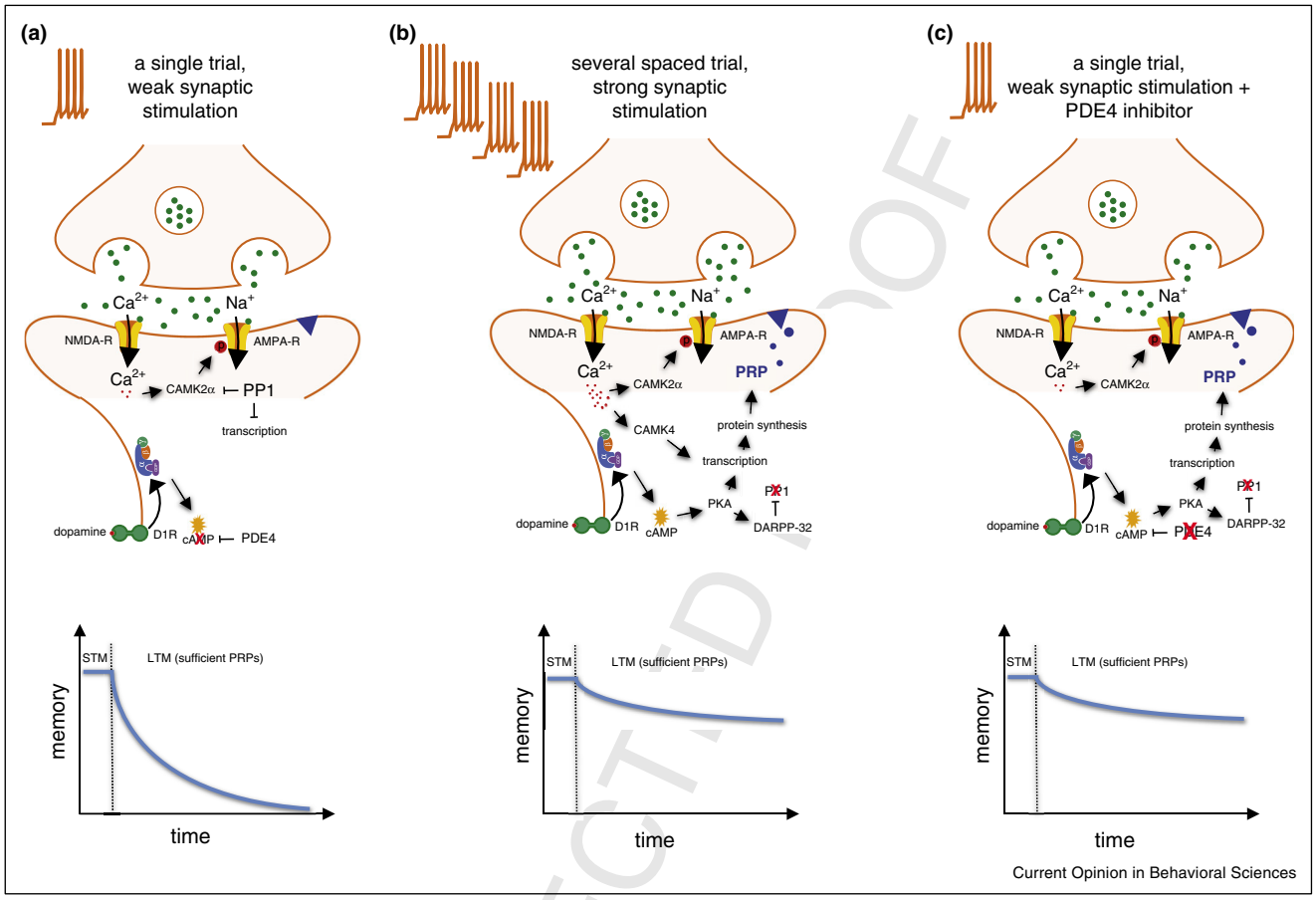
Figure 2



Persistence of memory — A model of the synaptic effects of training and PDE4 inhibitors: **(a)** A single trial (weak synaptic stimulation) leads to post-synaptic depolarization via AMPA receptors, activation of Ca2 + influx through NMDA receptors, activation of Ca2 + /calmodulin-regulated kinase 2α (CAMK2A), and the formation of a synaptic tag (blue triangle). CAMK2α mediated phosphorylation of AMPA receptors may contribute to the maintenance of synaptic plasticity, but this signalling event is counteracted by protein phosphase 1 (PP1) and memory cannot be stable [94•,95]. cAMP signals originating at the D1 dopamine receptor are counteracted by the cAMP-specific phosphodiesterase 4 (PDE4). **(b)** Multiple spaced trials (strong synaptic stimulation) lead to increased Ca^{2+} influx through NMDA receptors and voltage dependent Ca^{2+} channels (not shown). The Ca^{2+}/calmodulin-regulated kinase 4 (CAMK4) signalling pathway is activated leading to transcription of plasticity related genes via CREB [96]. Dopamine D1 receptors are activated strongly, leading to inhibition of PP1 via cAMP-activated protein kinase (PKA) phosphorylation of DARPP-32. PKA and CAMK4 support activity dependent gene-expression, de-novo synthesis of plasticity-related proteins (PRPs, blue dots), and synaptic capture of PRPs. Memory remains stable over time. **(c)** A single trial is predicted to lead to the formation of a stable memory when PDE4 is blocked pharmacologically. Mechanistically, this could be achieved by an increased cAMP signal originating at the D1 dopamine receptor, inhibition of PP1, activation of transcription via PKA and the extracellular-signal activated protein kinase (ERK, not shown), and de-novo synthesis and synaptic capture of PRPs. Memory remains stable over time.

likely that enhancement was primarily to memory encoding rather than consolidation or retrieval.

Studies of human spatial memory have a long history, but they received a very visible stimulus from Maguire's groundbreaking studies of London taxi-drivers who not only showed activation in hippocampal or para-hippocampal areas in carefully controlled PET and fMRI studies, but also structural changes associated with their skill and knowledge [75••,76,77••,78]. Notable was her groups' finding of a relative enlargement of the posterior compared to the anterior hippocampus as a function of the numbers of years that a London taxi-driver had been plying the streets of London [75••]. This effect was not seen in similarly experienced bus-drivers, who would likely have had as much time driving and equivalent exposure to non-relevant confounding factors (such as road traffic pollutants), but no professional need to get from one part of town to another than on a repeatedly prescribed route [79•]. Interestingly, new findings include that the spatial expertise of taxi drivers may compromise other forms of associative memory [80] and that the structural enlargement of the posterior hippocampus was not observed in trainee taxi-drivers who were unsuccessful

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in acquiring 'the Knowledge' as it is known colloquially in London [81••].

Physical exercise is also known to trigger neurogenesis in the dentate gyrus. Given this, it is intriguing that physical exercise in humans has recently been shown to increase the size of the hippocampus [82•]. However, this change was detected in the anterior rather than the posterior hippocampus as in the studies of Maguire, possibly because the dentate gyrus is larger in the rostral (uncal part) of the hippocampus, where there will therefore be more neurogenesis. Perhaps the difference between the two studies is that Kramer's group studied the impact of physical ('aerobic') exercise, which can also have a beneficial effect on stress as well as memory, whereas the changes in the posterior hippocampus seen in London taxi drivers are the result of spatial 'navigational' exercise. Interestingly, the Erickson *et al.* [82•] study included measurements of serum BDNF, a mediator of neurogenesis, finding an association with greater hippocampal volume.

These studies have been paralleled by imaginative virtual reality studies of spatial memory using fMRI [76] and even recordings of single-units in elective-surgery epilepsy patients during spatial and other tasks that have revealed striking category specificity [83]. New work by Itzhak Fried's group suggests both the possibility of voluntary control over single-cell firing in the medial temporal lobe and that direct entorhinal stimulation may even enhance memory [84,85]. This is preliminary but clearly very exciting. Recent work has also dissected the anatomical basis in humans of egocentric (precuneous) and geocentric (entorhinal cortex) aspects of the sense of direction [86,87]. Individual differences have also been investigated, with the report of a correlation between CA3 size and effective episodic memory of similar events [88•]. Episodic memory has, of course, a critical spatial element. Chadwick *et al.* [88•] suggest that in instances where there may be a partial failure of pattern separation in the DG, overlapping representations may occur within CA3. At retrieval, the presence of this representational overlap would then lead to a competitive pattern completion process. They speculate that a larger CA3 could aid retrieval, via an increased number of CA3 neurons or enhanced lateral connectivity within CA3, either of which could precipitate more efficient pattern separation. Whether this correlation is causal, in the sense that pharmacological or other procedures for enlarging CA3 could augment episodic memory is presently unclear.

A recent comprehensive review of both pharmacological and non-pharmacological approaches to cognitive enhancement in humans [89•] presents, at best, a mixed picture. The impact of a selected sub-group of pharmacological agents, including the NMDA receptor antagonist memantine, offers only the most limited evidence for reliably effective enhancement. Of a range of non-pharmacological routes including nutrition, physical exercise, sleep, meditation, mnemonics and retrieval training, it has to be recognised that larger effects are reliably seen. Mnemonics, such as the 'method of loci' rely upon the use of previously well-learned spatial information (such as the layout of a house — [77••]), while the dramatic but somewhat paradoxical effect of Karpicke and Roediger's (2008) retrieval training (see Ref [90]), a procedure now incorporated into University education in the form of regular 'quizzes' alongside lectures, may be mediated by maximising the opportunity for effective connectivity between the hippocampus and neocortex.

Conclusion

The remit for this article was spatial memory, and we end by noting that the use of human spatial memory is changing. One major change from as little as ten years ago is our daily interaction with the internet from an early age, and with this a greater visual than verbal culture in young people. The digital culture is impinging dramatically on how we find our way around (see — http://home.csis.u-tokyo.ac.jp/~ishikawa). People are also living many more years than before and this requires independent mobility to be sustained for longer. However, the use of accurate GPS enabled navigational devices may obviate the need for personal navigational or map-reading skills upon which previous generations have relied — indeed there is evidence that people who make extensive use of GPS equipment can actually be slower to navigate on their own [91].

We have noted that there are striking individual differences in how the human spatial navigation system is deployed, but in each of these it may already be near 'optimal' in normal adults. Some scholars look upon navigation as a lost art, citing the truly extraordinary skills of pre-literate people [92]. Our developing understanding of the spatial mapping and navigation system of the mammalian brain has nonetheless revealed the beauty and complexity of the neural network interactions involved in egocentric and allocentric navigation celebrated by the 2014 Nobel Prize. Such an evolved and complex set of systems and circuits may not be easily improved by modulation of synapses and signal-transduction pathways alone, and efforts to improve it pharmacologically may be rapidly corrected by endogeneous homeostatic mechanisms [93]. Pharmacological enhancement of spatial memory may only be valuable in adults already suffering memory loss (due to depression, stress, or age-related disorder such as mild cognitive impairment or dementia). Nonetheless, if such drugs could tip the balance towards an older person continuing to live independently for longer, or help in other everyday situations involving spatial memory, they would be enormously valuable.

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Conflict of interest statement

Nothing declared.

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